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ON INFANTILISM FROM CHRONIC INTESTINAL INFECTION

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On Infantilism from Chronic Intestinal Infection

CHARACTERIZED BY THE OVERGROWTH AND PERSISTENCE OF FLORA OF THE NURSLING PERIOD

A Study of the Clinical Course, Bacteriology, Chemistry and Therapeutics of Arrested Development in Infancy

BY

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New York
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1908

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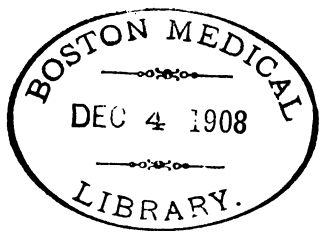

THE MASON-HENRY PRESS
SYRACUSE, N. Y.

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INFANTILISM

I PROPOSE in this publication to describe some of the leading features of an obscure affection of childhood with the study of which I have been for several years engaged but of whose nature I have only recently been able to form a reasonably satisfactory conception. This pathological state is marked by a striking general retardation in the growth of the body implicating the skeleton, the muscles and the organs, while permitting a relatively fair development of the brain. The material on which the present description is based consists of five cases of intestinal infantilism which I regard as typical and fully developed examples of this distinctive state. And in addition to these cases I have studied five others of shorter duration and subacute course, which I am disposed to consider as instances of intestinal infection capable of giving rise to pronounced infantilism when the former condition has persisted through many months. With the exception of two of the cases comprising these two groups, I owe to Dr. L. E. Holt the opportunity to study these patients. He has helped me by freely placing at my disposal his full clinical notes and by

giving me access to his patients. In several instances the patients have been observed by Dr. Holt and myself conjointly during a period of years under varying dietetic conditions. The definite character of the symptom-complex about to be described has long been recognized by Dr. Holt, who has interested me in the present investigation.

I am also under obligations to the Rockefeller Institute for Medical Research, especially during the past year, for aiding me with facilities for engaging in the extremely complex bacteriological problems with which this study was beset. I am especially indebted to Mr. A. I. Kendall, Fellow of the Rockefeller Institute, for technical help.

It has not been possible to investigate with equal thoroughness all the cases of intestinal infantilism that constitute the basis of this publication. In some instances attention has been given especially to certain limited aspects of the pathological problem, while in other cases study has been especially focused on other features; but in three instances the investigations have had a wider and more representative aim. In two of these three instances the patients have been under my personal observation during periods of many months, and through close attention it has been possible to detect and to follow with unusual detail numerous manifestations of the morbid process. I shall

not undertake in the present publication to give full individual histories of the cases observed, but shall merely give very brief outlines embodying the chief clinical data, and to these outlines such references will be made from time to time as may serve to illustrate the various points under discussion.

CASE I. Male, aet. 8 years. Older sister in good health. Normal infancy with average growth. During third year reached weight of 31 lbs. At this time irregularities of digestion, especially periods of diarrhoea with mucus. Gradual loss of weight, increasing abdominal distension, carbohydrate intolerance and fat diarrhoea. Between third and seventh years weight did not exceed 31 lbs. Usually losses in summer, gains in winter, weight usually between 25 and 28 lbs. Moderate anaemia. Increasing lassitude. Drowsiness during day. Walking difficult. Rapid onset of fatigue. Peevishness, emotional instability, slight signs of rickets. Appetite nearly always keen. Many dietetic experiments tried between third and seventh years with little success. Movements several daily, soft, voluminous, gray, fatty, gaseous, odor indolic, reaction usually slightly acid or neutral. Mucus variable, at times very abundant, in masses on surface or mixed with feces. Urine rich in indican and phenol. Aromatic oxyacids not markedly excessive. During last year gradual decrease in indican. Reactions for indolacetic acid very marked. November, 1907, weight, 25 lbs.; height, 36 ins. Careful dietetic and hygienic measures instituted. Next four months slight gains and losses in weight but no material improvement in weight though decided improvement in character and frequency of stools and diminution in signs of intoxication. From March, 1907, to July, 1908, uninterrupted somewhat uneven gain in weight to 31 lbs. Also gain in height (about 1½ inch). Movements became entirely normal in color, consistence and frequency. Urine shows striking reduction in putrefactive products. Mental and emotional condition greatly improved. Expression animated. Physical activity greatly increased, walking fair for considerable distances. Abdominal distension much diminished. During past six months there has been a radical alteration in the bacterial flora of the large intes-

tine, marked by the establishment of *B. lactis aerogenes* and *B. coli*. Still remains very sensitive to carbohydrates, even a slight increase being quickly followed by large fermentative movements. Under such conditions the child ceases to gain weight and there is a return of coccal forms in the feces, but *B. bifidus* cannot be detected. Such a temporary interruption in growth occurred during August, 1908.

CASE II. Female, aet. 9 years. Two older children, always well. Normal infancy, nursed during early months. At end of second year irritant medication followed by gastritis lasting several days and only slowly subsiding. Present illness dates from this. Slight signs of rickets somewhat antecedent to the gastritis. By third year nutrition was impaired and development became much retarded. Child markedly undersized, head slightly rachitic, digestive tract irritable, carbohydrates very badly tolerated, fat absorption much impaired, abdomen much distended. By fourth year walking still very imperfect and child much undersized. Weight at this time not recorded, but nutrition much impaired and remained so during fourth, fifth, and sixth years. Throughout this time there were moderate anaemia, fat diarrhoea, grayish, voluminous, gas-holding, indolic stools. Urine regularly gave intense indican reactions. Ethereal sulphates, phenols and aromatic oxyacids regularly much increased, micturition often extremely frequent. During this entire period emotional instability, peevishness, great physical langour, walking quickly followed by fatigue. In sixth year, after more than a year of careful regulation of diet, gradual improvement in nutrition, and gain in physical strength with slow disappearance of neuromuscular disorders. Simultaneously gradual diminution of putrefactive products in urine and pronounced improvement in feces, which became formed, colored, of normal fat content and nearly free from indol and phenol. Gradual appearance of *B. lactis aerogenes* and *B. coli* in large numbers in the feces. At six and one-half years weight rose to 45 lbs. During next year gained 2 lbs. During following year gained 10 lbs., to 58 lbs. During last six months gained 7 lbs. with rapid gain in stature. Onset of epileptiform seizures during this period with return of putrefactive products in urine.

CASE III. Female, aet. about 7 years. Under observation together with Dr. L. E. Holt for past 3 years. When first seen, greatly emaciated. Abdomen much distended, superficial veins distended markedly. Skin white and wrinkled. Anaemia mod-

erate. Head slightly rachitic, well developed. Extremely emotional and peevish, but intelligent. Movements voluminous, acholic in appearance, usually two or three daily; odor putrefactive (indolic), reaction usually neutral or acid. Fatty acid crystals very abundant, mucus variable, indol regularly present, phenol sometimes. Diarrhoea easily provoked by use of carbohydrates. Urine frequently voided, indican abundant, phenol and aromatic oxyacids excessive. Record of weight lost, but child much beneath average weight for about one year before observation. Loss in weight dates from middle of third year, when irregular diarrhoea and large movements became chronic. During first two years under observation only slight gain in weight, but some improvement in movements, which became seldom diarrhoeal but remained voluminous. During past year more rapid gain in weight, but still markedly under weight. Case closely resembles Case I, but infantilism is somewhat less pronounced in degree. Conditions for dietetic treatment much less favorable than in Case I. Outlook is now for decided permanent retardation in growth. Child was normal at birth and for first two years.

CASE IV. Male, aet. 3 years. Normal weight at birth, nursed 6 weeks. Modified milk. Did well first year. Then irregular intestinal troubles, diarrhoea with mucus. Marked anaemia gradually developed (Hb 35%) with great abdominal distension. Appetite poor. Peevishness. Slow loss in weight from 16th month. Movements gray, voluminous, pasty. Fatty acid crystals extremely abundant, indol, but no skatol; phenol at times. Urine, much indican usually, also excess phenols and aromatic oxyacids. Many experiments with diet; peptonized milk; kumyss, egg white, rare scraped meat, Nestle's Food, etc. Appetite capricious. Weight at 20 mos., 16 lbs.; height, 30¾ inches; at 27 mos., 15 lbs. Gradually gained to 17 lbs. then acute slight enterocolitis for 4 or 5 days. Gradually lost weight to less than 15 lbs. At 33 mos., weight, 16½ lbs.; height, 31 inches. Hb. 34%. Very slow improvement in weight and movements. Now (3 years) 18 lbs. and Hb. 61%. Appetite never satisfied, tongue clean and red. Abdominal distension persists. Spirits improved. Tendency to diarrhoea from carbohydrates continues. Milk remains basis of diet. Improvement probably delayed by impracticability of following patient closely.

CASE V. Female, aet. 9½ years. Patient of Dr. L. E. Holt. Third of four children; others healthy. Partly nursed 3 mos., did poorly, was weaned. Fed on sterilized milk, cream, lime-

water rest of first year. Did only fairly well; fat but pale. Measles at 18 mos., mild. Vaccinated at 2 years; sore healed normally. With vaccination, vomiting and fever. Troubles of digestion rather marked ever since. Vomiting and fever rarely, but tendency to soft movements and diarrhoea with occasional constipation. During fifth and sixth years marked irregularities of bowels associated with efforts to increase diet. Seizures of loss of appetite, headache and loss in weight, light-colored stools, lasting several weeks. Marked abdominal distension, tongue coated, breath not good. Food, milk, a little bread, beef juice. With every effort to give carbohydrates child shows digestive derangements after a few days. At 5½ years, weight, 21¾ lbs.; height, 35 inches. Very pale, spleen, liver, glands palpate normal, tongue slightly coated, abdomen smaller than formerly; a small, pathetic, delicate little child with no animation. Sometimes does not walk for 2 or 3 months. Remained very much under weight until nearly 9 years old, with periods of great abdominal distension and continued intolerance for carbohydrates and fats. Constipation at times, owing probably to milk diet. Facial neuralgia frequent, anaemia marked. Great listlessness. Walks only a few steps about the house. Appetite always excellent now, could take much more but cannot tolerate increased food. Milk agrees best. Diet somewhat enlarged with barley broth, baked potato, butter, tapioca pudding. On this diet good gain in weight lately. Gain to 33 lbs. at 9½ years and rather rapid gain in height to 38¼ inches. Head 20 inches, somewhat rachitic, flat type and large parietal bones. Morbid appetite for chalk, dirt, cigar ashes, pencils, etc. Urinary indications of intestinal putrefaction but slight. Anaemia still marked. This case of intestinal infantilism is of somewhat different type from the others in this group. Less indication of ordinary indolic putrefaction, more tendency to anaemia. Uncertainty as to pathology from standpoint of bacterial flora.

The symptom-complex which I wish to describe is so clearly definable that few physicians with a practice among children will fail to recognize a few instances of this unmistakable and extreme manifestation of a morbid nutritional process. I shall group under the follow-

ing heads the facts and views which I desire to present.

1. The Symptoms and Signs of Intestinal Infantilism.
2. The Bacterial Flora of the Intestinal Tract in Cases of Infantilism.
3. The Urinary Expressions of the Infection underlying Infantilism.
4. The Pathology of Intestinal Infantilism.
5. The Acute and Subacute Infections leading to the Establishment of Intestinal Infantilism.
6. Mild Types of Intestinal Infantilism.
7. The Sequelae and Prognosis of Intestinal Infantilism.
8. The Therapeutic Modification of the Bacterial Conditions in Intestinal Infantilism.

The Symptoms and Signs of Intestinal Infantilism

The patients comprising the group of the type of fully developed infantilism which I desire to describe varied from four to six years of age at the time when they first came under observation. In each case the child had been ill for one year or longer at the time of its first observation by Dr. Holt or by myself, and had suffered from pronounced irregularities referable to the digestive tract. In each case there was a history of periods of disturbed

nutrition with loss of weight alternating with periods of improvement in nutrition and gain in weight. But these variations ultimately culminated in each case in a state in which there was apparently a complete arrest of development, and although obvious symptoms of digestive disturbance, such as diarrhoea, were checked by suitable treatment, there remained an arrest in growth and the utmost difficulty was experienced in securing any noteworthy increase in weight.

The clinical features characteristic of pronounced infantilism may be divided into two groups, the chief or essential clinical features and the minor or accessory features.

The chief or essential clinical features are the following: (1) an arrest in the development of the body; (2) the maintenance of mental powers and fair development of the brain; (3) marked abdominal distension; (4) moderate grade of anaemia; (5) rapid onset of physical and mental fatigue; (6) various obtrusive irregularities referable to the intestinal tract. These features may be considered in turn.

(1) *Arrest in Development of the Body.* The arrest in development is the most striking feature of these cases. In Case I the patient at the age of seven years weighed only 25 pounds[1]

[1] Holt gives the weight for a boy of two years as 26.5 pounds. The weight at seven years should not be far from 50 pounds.

and had a height of only 36 inches.[1] In Case V the patient at the age of nine years weighed only 29 pounds. In this case the child was first observed at a time when some improvement had set in, a gain of two pounds having been made in the course of the past year, but previous to this time the patient had for some time remained in a stationary condition as regards weight and development. In Case II there was a period of about two years (from the third to the fifth year) in which there was a striking arrest of development, and the maintenance of a nearly stationary weight despite the fact that the utmost care was taken to insure dietetic conditions favorable to an improvement in growth. In the two remaining cases exact data are lacking, but in both instances retardation of growth was a striking feature during a long period of time. In several instances it was noticed that there was a slight tendency to improvement in weight during the winter months, this tendency to improve being more than overbalanced by losses made during the summer. These losses in weight were always attributable to an increase in disturbances referable to the intestinal functions and were commonly associated with diarrhoea. This diarrhoea was, however, not necessarily very pronounced or of long dura-

[1] Thirty-five inches is the height given for three years.

tion, and often consisted rather in an excessive softening of the intestinal contents and increase in mucus than in an acute watery diarrhoeal condition

(2) *The Maintenance of Mental Powers and Fair Development of the Brain.* It is noteworthy that despite the retardation in the general development of the organism, the brain is fairly well developed in all of the cases of infantilism under observation. Thus in Case I, although the height was only 36 inches and the weight 25 pounds, the circumference of the head was 20 inches.[1] Entirely comparable conditions were noted in the other cases. The intelligence of these patients was in every instance good, and contrasts very strikingly with the bad physical development. Of course these children are all defectively educated owing in part, at least, to the physical retardation which makes it inadvisable or impossible to secure even the ordinary educational opportunities. It is noteworthy that in all of these children there was a certain slowness of mental action and perhaps a somewhat greater thoughtfulness than is usual in children of their age. In replying to questions these children have often shown some irritability and peevishness, and in several instances I think there is no

[1] Holt gives 19.7 inches for the circumference of the male head at four years; 20.5 inches at five years.

doubt that the mental processes subserving self-preservation were more than usually acute for children of their ages. It is possible that this was the result of the isolation to which all of these patients had been subjected and of an inability to enter into the play of children of the same age. The necessity for living very carefully and obeying the directions of the physician and nurse has tended to make these children somewhat introspective as regards their own ailments and to form the basis of what might, with increasing consciousness, develop in after life into a hypochrondriacal condition. In all of the patients periods of langour have been very noteworthy during the time of arrested physical development. Frequently for hours at a time they show little or no desire to play or to speak and their faces at these times look pinched and distressed. There has been no difficulty in any of these cases in teaching the children to be cleanly, and there is no doubt that what they have lost in the direction of spontaneity and playfulness, as the result of disease, has been in a measure compensated by an improved self-control, which, in the case of diet, has come to amount almost to automatism.

(3) *Marked Abdominal Distension.* Marked abdominal distension, due in part to a distension of the colon with gas and probably

also to distension of the small intestine, has been a feature of these cases. The distension has varied somewhat from time to time, but there have been long periods in each case in which the distension showed little variation and a return to normal abdominal conditions was never witnessed. As these patients gradually improved in physical condition under suitable dietetic treatment, the distension gradually became less. This condition of distension, when once established, is not necessarily accompanied by any intestinal or gastric flatulence in the sense of actual passing of considerable quantities of gas. It appears that the abdominal distension was preceded in each case by a period in which gas formation had been active and flatulence pronounced, but that after a time partial paralysis of the gut sets in, which permits the accumulation of gas even though the latter be not necessarily formed in great excess. The abdominal veins are frequently markedly dilated, especially over the upper part of the abdomen.

(4) *Moderate Anaemia.* In all of the five cases of infantilism which were studied, moderate anaemia was a feature. The haemoglobin was diminished to 75-60 per cent. in Cases I, II and III without a corresponding diminution in the number of red blood cells. In two instances, however (Cases IV and V), the

anaemia was considerably more pronounced, and in Case V was a long persistent feature of the disease. In the latter instance the haemoglobin was at one time only 22 per cent., and there was a moderate diminution in the number of red blood cells. In all of these cases there is reason to think that the volume of blood is at least moderately below what it should be for a child of the same weight. This suspicion is based on the pallor of the body and the extremities, which may be much out of proportion to the fall in haemoglobin. The white blood cells were examined in Case I. No noteworthy departures from the normal were noted.[1]

Leucocytes 5000

Small mononuclears	33%
Large mononuclears	1%
Eosinophiles	1%
Polymorphonuclears	62%
Transitionals	3%

An examination made on April 22, 1908, gave the following:

Leucocytes 6000

Small mononuclears	35%	Polymorphonuclears	51%
Large mononuclears	2%	Myelocytes	6%
Eosinophiles	3%	Transitionals	3%

(5) *Rapid Onset of Fatigue.* A characteristic feature of these cases of infantilism is the rapid onset of muscular fatigue. Indeed, it would probably be more accurate to say that the muscles are never thoroughly rested

[1] An examination made Dec. 30, 1907, by Dr. Baldwin gave the following results:

and that a state of fatigue is chronic. The older children, at the height of the developmental arrest, are unable to walk more than a few blocks without being thoroughly tired. They are also unable to walk up and down stairs. Learning to walk is a slow and discouraging process. In Case II the child did not learn to stand until it was more than four years old, up to which time it crept languidly on the floor. During the fifth year it learned to walk with great difficulty. Essentially the same condition existed in Cases III, IV and V. It is to be noted that the muscles are soft and flabby in these cases of infantilism. The readiness with which mental fatigue comes on has already been commented upon. As will be seen later in a discussion of the pathology of this condition, there is good evidence for believing that both the muscular and mental fatigue are the result of a chronic intoxication.

(6) *Disturbances of Intestinal Function.* One of the most striking and characteristic features of infantilism has to do with the disturbance incidental to intestinal function. Although such disturbances may be reduced to a minimum through very careful feeding, the dietaries of these children are usually such when they come under the observation of physicians that they show very obvious disorders of function. Diarrhoea was a feature of all of the cases with

which this report deals. Pronounced watery diarrhoeal attacks are, however, comparatively rare. Much more frequent are the disturbances manifesting themselves by the appearance of soft stools containing an abundance of neutral fat, soap and fatty acid crystals. The excess of fat is often sufficiently great to constitute a condition of true steatorrhoea, if thereby we imply a loss of fat serious to nutrition. During a part of the time the stools are not of abnormal frequency. Nevertheless they contain an excess of fat unless the diet is especially regulated with a view to reducing its fat content. During exacerbations of the diarrhoeal disturbance the patients are in especially poor condition, losing weight and suffering from cold hands and feet and showing a pinched appearance. These diarrhoeal disorders, though often of short duration, may also cause marked prostration, and on many days patients are so much enfeebled as to get about with greatly increased difficulty. With the cessation of the diarrhoea there is a tendency to rapid recovery, although a loss in weight of half a pound or a pound may not be regained for several weeks. The details relating to the morphological and chemical characters of the intestinal contents will be discussed in another section of this paper.

Among the minor or accessory clinical features observed in our cases of infantilism are to be included sweating about the head during sleep, excessive appetite, somewhat excessive thirst and consequent increase in the urine, various indications of nervous instability and an habitually subnormal temperature with cold and pale hands and feet. In three of the cases (Cases I, II and V) the sweating, especially of the skin of the head, was for a time well marked, but this symptom very soon disappeared with return of strength. An excessive appetite, at least at certain times, was a feature in all the cases. Occasionally, especially during the diarrhoeal periods, there is loss of appetite. But the maintenance of a large appetite is a feature in these cases. A similar readiness to take food has been noticed in the subacute affections which, beginning in early infancy, lead to the state of infantilism. The abnormal, sometimes even voracious, appetite is probably due to the condition of chronic enteritis which exists in these patients and is probably similar in its origin to an increase in appetite observed in some neurasthenic adults. The nervous instability is shown in some of these patients by rapid variations in temper from insignificant causes. In one instance (Case I) there was also a tendency to urticarial outbreaks, which occurred from time

to time without definitely assignable cause. In another case (Case II) there developed attacks of *petit mal* which, as will afterwards be more fully stated, gave way to epileptiform seizures of *grand mal.*

In four of the five cases of infantilism there were very slight indications of rickets, but it may be said in general that the signs of rickets, if present at all, do not form part of the symptom-complex at present under discussion. Outside the present group I have seen well-marked instances which showed no signs of rickets. There are no striking pulmonary or circulatory peculiarities in these cases. The pulse is usually regular when the patients are quiet, of low tension and small in volume. The pulse is unduly accelerated by slight activity or slight exterior nervous stimuli. Abnormalities of the spleen, liver or thyroid have not been detected. In one case (Case I) there was slight enlargement of the posterior cervical glands. A status of blood occurs readily in artificially congested areas of the skin—an effect like that of the so-called meningeal streak being readily produced. The tongue is apt to be somewhat more red than normal, and the papillae swollen, but in none of our cases was there any denudation of epithelium or any indication of the occurrence of geographical tongue. The tongue

is at times slightly swollen and on its edges marked by impressions of the teeth.

The Bacterial Flora of the Intestinal Tract in Cases of Infantilism

The difficulties that lie in the way of the adequate understanding of the bacterial conditions of the digestive tract have been in general so numerous as to discourage attempts to investigate the nature of the flora in chronic diseases of the intestine. Of these difficulties there are three which are specially obvious,—first the multiplicity of the floral types; secondly, the uncertainty of cultivating the really dominant organisms; third, the difficulty of obtaining for study those products of symbiotic bacterial action which are truly representative of the decompositions which occur in the intestine. Although efforts have been made in the present study to overcome these obstacles, these efforts have been only in part successful. Still it is fair to say that the methods of investigation employed have yielded a helpful if not satisfying conception of the processes that hold sway in the digestive tract in the state of infantilism. It is not intended to discuss in detail in the present communication the methods of investigation employed, nor to describe fully the characters of the organisms which have been found to dominate the intestinal flora. In

many directions the details concerning the nature of the organisms which have been found to be dominant in these cases have not been established with sufficient precision. Knowledge is especially scanty at the present time in regard to the biochemical activities of certain of the organisms that have been found to dominate the intestinal tract in these cases. Especially is knowledge lacking in regard to the products of symbiotic growth of the chief organisms observed. For the present purpose it will suffice to state that the methods of bacterial study which have proved most serviceable in this investigation have been (*a*) the study of the Gram-stained fecal fields; (*b*) the study of the sediments of the sugar-bouillon and plain bouillon tubes after inoculation with the mixed fecal flora; (*c*) a variety of aerobic and anaerobic cultural procedures involving the use of many kinds of media made necessary by the difficulty of growing certain species of bacteria in pure culture.[1] In these studies bacteria were obtained not only from the feces, but from material derived by the use of calomel catharsis from the upper levels of the intestine. Such catharsis failed, however, in general, to show radical differences between the bacterial

[1] In the case of one of the microörganisms to be described (B. infantilis) careful studies were made of the products of growth. The results will be separately published in conjunction with Mr. Kendall.

types so obtained and those obtained from the feces, despite the fact that coccal and Gram-negative forms were usually obtained in greater abundance from these upper regions. A distinction of greater significance was found to relate to differences noted between the bacteria derived from the fecal masses and those derived from the mucous membrane of the intestine. To these differences further reference will be made. About three years ago, while studying a patient with intestinal infantilism, I observed that the Gram-stained fecal fields were regularly made up of almost exclusively Gram-positive microörganisms. These positive bacteria were almost exclusively slightly curved rods from two to three microns in length and about one-half micron in diameter. The ends of these rods were sometimes rounded and sometimes pointed. Morphologically similar fields are sometimes observed in normal breast-fed children as has been noted by Tissier, Moro and others. But while it may be regarded as entirely normal to find organisms of this character in a certain proportion of healthy, breast-fed children, it was surprising to find organisms of this nature as the dominant bacteria in children five or six or even eight years of age. The study of normal children at these ages has failed to give any such pictures as those which I have noticed in the

group of cases of infantilism now under consideration. Similar organisms have, however, been observed in the Gram-stained fields in a group of young children fed on cow's milk and suffering from pronounced acute or subacute gastro-enteritis. As I shall point out later, it appears highly probable that the cases of chronic infantilism have their origin in intestinal disorders of very early life characterized by the presence of dominant Gram-positive flora of the kinds above described.

The nature of these Gram-positive organisms, which constitute so persistent and dominant a feature in our cases of infantilism when at the height of their development, has been involved in much obscurity. In 1900 Escherich described a fatal hospital epidemic among young children in which he observed that the stools in certain instances consisted almost wholly of Gram-positive rods, morphologically of the type just mentioned. He gave to this condition the name of blue bacillosis (*Blaue Bacillose*) to signalize the fact of the Gram-positive nature of the bacilli in question. Escherich also observed that when the bacterial stools of the children in question were transferred to ordinary culture media, there was no growth of Gram-positive organisms, but only of the Gram-negative colon-like bacteria which were an insignificant feature in the field. This latter observa-

tion I can confirm, and it is only by the use of very careful cultural methods that it has been possible to obtain some insight into the nature of the Gram-positive organisms seen in these fields. As will be pointed out in what follows, there are three kinds of organisms which may give rise to appearances in the Gram-stained field similar to those occasioned by the presence of the Gram-positive, slightly curved or straight rods which have been mentioned. These organisms are the *Bacillus bifidus* of Tissier, the *Bacillus acidophilus* of Moro and a hitherto apparently undescribed organism which will be called here *Bacillus infantilis*.

That the *B. bifidus* of Tissier, or an organism bearing an extremely close resemblance to it, is present in large numbers in the intestinal contents of our cases of infantilism is indicated in part by the study of the sediments of the sugar-bouillon fermentation tubes and in part by other cultural procedures. I observed several years ago that when the mixed fecal flora from a case of infantilism or from certain instances of acute or subacute enteritis in infants were inoculated into sugar-bouillon fermentation tubes (lactose, dextrose and saccharose) there was a very abundant growth in the tubes of bifid organisms, either growing separately or in groups in which individual

bifurcating organisms are fused together so as to give rise to varied pictures. A study of the fermentation tube sediments not merely served to attract attention to the occurrence of bifid types of bacteria in the intestinal contents, but also drew attention to certain other forms of bifid microörganisms that may occur under the same cultural conditions and to the importance of certain coccal forms of bacteria. It will be convenient to discuss the dominant types of organisms in our cases under the following heads: (1) organisms of the *B. bifidus* type; (2) organisms of the *B. infantilis* type; (3) coccal forms.

(1) *Organisms of the Bacillus bifidus Type.* Although it has been easy to obtain from the fermentation tubes very abundant and dominant growths of bifid, lactic acid-producing microörganisms corresponding to the morphology of *B. bifidus* of Tissier, considerable difficulty was encountered in obtaining these organisms in pure culture. Mr. Kendall has now succeeded in growing the organisms in question on various media under anaerobic conditions. The organisms were derived not merely from the stools of patients with infantilism, but also from the stools of certain cases of subacute enteritis in infants which have already been alluded to as presenting fields made up almost exclusively of Gram-positive bacilli. The organisms in ques-

tion grow on dextrose-agar plates as lenticular or helmet-shaped colonies and on anaerobic agar slants present beaded, grey, shining colonies slightly opaque or translucent. Morphologically, the organisms present the typical Y-shaped or bifid form. They are Gram-positive and vary in size from two to four microns in length and from six tenths of a micron to one micron in width. They are sometimes apparently slightly motile. In fermentation tubes and associated with other bacteria they grow well in dextrose, lactose and saccahrose bouillon, but especially well in the two former. They produce lactic acid and are capable of maintaining themselves at a considerable grade of acidity. For this reason they have been classed as acidophile bacteria. The justice of regarding them as strict acidophile organisms may, however, perhaps be questioned, since in the absence of interfering organisms they may grow well in sugar-bouillon in which the acidity is in large degree neutralized by the presence of calcium carbonate. It appears rather that they are capable of withstanding a higher degree of acidity than some other intestinal microorganisms, as, for example, colon bacilli, and are therefore able to thrive when the colon bacilli are no longer able to reproduce themselves in consequence of the excess of acid. These organisms coaggulate milk, but do not

peptonize it. They do not grow on gelatin. Although they may be regarded as anaerobic organisms, it is true that after a time they grow to the surface in agar stick cultures and may even cause a slight elevation of the surface of the agar. These organisms do not always show bifurcation, and under certain cultural conditions tend to develop rarefication of their protoplasm in spots, so that the Gram-stain is retained irregularly, giving rise to punctate forms of bifidus. This punctate form of bifidus may be plain or may undergo branching.

Successful plate cultures indicate that the bifidus type of organisms is very abundantly represented in the feces of certain cases of intestinal disorder, including not only cases of infantilism, but the subacute conditions already mentioned. They have been studied by Mr. Kendall with especial care in Case I of the infantilism group and in some instances of subacute intestinal infection characterized by Escherich's blue bacillosis. I have found them also in Cases II, III and IV. It is impossible at present to say just how large a proportion of the organisms in the cases mentioned belong to the *B. bifidus* type, but the plate cultures indicate that they are prominent all the time, though sometimes more largely dominant than at others. With the exception of Case I of

our group of infantilism patients, the presence of *B. bifidus* in large numbers in the stools has been commonly inferred from the bifid forms found in the fermentation tube sediments and from the morphological characters of the organisms in the smears from the stools, rather than from cultures on plates.

It seems worth noting that in the studies made from mucus obtained from the stools in Case I, Case II and in one of our patients with subacute blue bacillosis, sugar-bouillon fermentation tubes inoculated with carefully washed mucus have shown the development of a great abundance of bifid forms, apparently in almost pure culture, whereas inoculations made from the fecal material from the same cases showed a far less rich growth as well as the presence of other varieties of micro-organisms.

(2) *Organisms of the Bacillus Infantilis Type.* The organism to which the name *Bacillus infantilis* has been applied was first noticed by Mr. Kendall while working on the cases of infantilism described in this paper. This organism, or type of organism—for there are several variants—occurs not rarely in the stools of breast-fed and bottle-fed infants. It has been isolated also from a number of children ranging from two to seven years of age, and has been obtained from one adult. Under

normal conditions the number of organisms of this type growing upon nutrient sugar-agar plates is not great. In fact it is frequently difficult to obtain cultures. In certain cases, however, especially in those showing the Gram-positive fields of the blue bacillosis type, the number is greatly increased, judging from their abundance in plate cultures.

In stained stools, the organisms appear as rather thin, Gram-positive rods, agreeing in size with Tissier's *B. bifidus communis*. The *B. infantilis* has not been observed to occur with pointed ends, as is the case with at least some varieties of the *B. bifidus*. The organism forms spores which are central (but occasionally terminal), causing a slight swelling of the rod. In the vegetative state *B. infantilis* as studied by Mr. Kendall is actively motile. It usually occurs singly or in pairs, but under certain conditions, particularly in fluid media, may form chains of several elements. (In length it varies from 2.5—3 microns, in width from 0.5—0.75 microns.) Occasionally one sees distinct branches in anaerobic dextrose agar. *B. infantilis* is ordinarily isolated from anaerobic plates, although it has been obtained without difficulty in some instances when grown under aerobic conditions. After the first generation upon artificial media, it grows readily in the incubator at body temperature and much less

readily at 20° C. The submerged colonies are of two types, one lenticular and yellowish, the other rather irregular in outline and woolly in appearance. The surface colonies are usually dull and have a tendency to spread. The surface growths are gray. There are two types of growth upon agar. The first is almost invisible and is limited largely to the condensation water. The second is more vigorous and spreading. Spores are readily formed upon the surface of slants, usually within 48 hours. The bacilli in the spore stage are slightly spindle-shaped, frequently with a deeply staining Gram-positive granule at either end of the rod, more usually at one end only. Many cultures produce a mucin-like substance. In fluid media spore-formation is delayed and is frequently absent. In sugar-bouillon (dextrose, lactose) there are two types of growth. The first corresponds to the form that grows poorly on agar, showing a slight sediment with usually a transient turbidity and no pellicle; the second type of growth is indicated by a moderate turbidity and the development of a sediment and usually a pellicle. Upon plain broth there is no turbidity and in many strains a pellicle is formed. The bacilli from the sediment are usually elongated, show irregular or punctate staining and may occur singly, in pairs or less commonly in chains. Milk is not coagu-

lated by *B. infantilis*, nor is there any evidence of peptonization. The reaction is usually slightly alkaline after four to seven days, although this alkalescence is not marked and may be absent. In fermentation tubes the organisms produce acid, but no gas in dextrose or lactose or saccharose. The acid production in lactose is relatively slight. On gelatin there is a very slight growth and frequently none at all. There is no liquefaction. *B. infantilis* inhibits the gas production of the colon bacillus when the two organisms are grown in dextrose or lactose bouillon, the gas production of the colon bacillus being sometimes restricted to the extent of 80 per cent. The colon bacilli grow at first more rapidly, but soon the advantage thus obtained is permanently lost and *B. infantilis* distinctly checks the further growth of *B. coli*. *B. infantilis* forms neither indol nor skatol. It forms volatile bases in great abundance, chiefly ammonia. We have found methylamin among the products.

It is impossible to state at present to what extent the Gram-positive rods observed in the fields obtained from children with infantilism consist of *B. infantilis*.

(3) *Coccal Forms.* The third group of organisms consists of coccal forms, the relation of which to one another is still obscure. In our cases of infantilism, Gram-positive coccal forms

have at times been abundant, and even when not prominent in the fecal fields may grow freely in the sugar-bouillon fermentation tubes. They consist chiefly of larger and smaller diplococci or coccobacilli corresponding closely in morphology and cultural characters to the enterococcus of Thiercelin or the *Micrococcus ovalis* described by Hirsch-Libmann. The enterococcus forms acid on dextrose, lactose and saccharose and coagulates milk.

In one of our cases of infantilism associated with profound anaemia (Case V) the fecal fields showed very large numbers of small, Gram-positive cocci. These were found especially in certain parts of the stools where they were seen to the exclusion of other organisms. It was especially in the mucus and about the epithelial elements that these organisms were noted in such abundance and concentration. In respect to these organisms Case V presents an exception to the remaining four cases in the infantilism group. The character of the coccal forms occuring in this case have not as yet been thoroughly studied.

It is worthy of mention that neither the *B. bifidus* forms nor the *B. infantilis* forms that have been isolated from our cases of infantilism have exhibited pathogenicity when injected into guinea-pigs. In Case I it was observed that the relative proportion of organ-

isms of these three types which appeared upon anaerobic plates varied a good deal from day to day without apparent cause.

As regards the presence of organisms of the *B. coli* and *B. lactis aerogenes* groups, it may be stated that such organisms are infrequent in the feces in our cases of infantilism, when they are in their most pronounced stage. This is true also of the subacute cases of intestinal infection already mentioned. Indeed in this latter group of cases it is the rule to see Gram-positive fields, wholly free from organisms, suggesting either *B. lactis aerogenes* or *B. coli.* It is probably owing to the almost entire or the complete absence of these normal intestinal inhabitants that the gas production in the fermentation tubes inoculated with the mixed fecal flora from the cases of infantilism at their height, has been slight or lacking. These conditions, however, hold true only for our cases in their most highly developed form. As recovery has set in it has been observed in Cases I, II, III and IV that with improvement in nutrition there has been a relative decrease in the number of Gram-positive bacterial elements in the feces and a corresponding development of Gram-negative forms corresponding to *B. lactis aerogenes* and *B. coli.* In the case of infantilism (Case II) in which the greatest improvement in nutrition has been observed,

B. lactis aerogenes has lately been isolated from the plates in great numbers. In this case an increase in gas production has gone hand in hand with the establishment of the normal flora in the feces. It may also be remarked that in this case the improvement in nutrition and the gradual restoration of the normal flora occurred with comparative rapidity during a period of eighteen months, and not until after the child had reached the age of eight years; previous to this recovery had been extremely slow during three years. It should also be stated that in this same case (Case II) the disappearance of Gram-positive organisms of the *B. bifidus* type was associated with the great falling off in the growth of *B. bifidus* in the fermentation tubes. *B. bifidus* was represented in the fermentation tubes not by well-staining bifid forms, but by small punctate rod forms apparently atrophic in character, though still capable of cultivation. Finally it should be stated in reference to Case II that with the disappearance of organisms of the *B. bifidus* type and the reëstablishment of *B. lactis aerogenes* and *B. coli,* the intestinal tract began to show excessively large numbers of *B. aerogenes capsulatus.* This organism had not before been noted as a prominent inhabitant of the intestinal tract, and was indeed probably present in only small

numbers, if at all, previous to the eighth year of life.

The Urinary Expressions of the Infection underlying Infantilism

Considerable attention was devoted to the characters of the urine in our cases of infantilism, especially in Cases I, II and III. In Case I the specific gravity of the urine ranged from 1010 to 1015, and the volume of urine was habitually large—800 c.c. to 1100 c.c. In Case II, during the time between the fifth and ninth years of life, the specific gravity of the urine ranged usually from 1010 to 1018. The volume of urine varied from 600 c.c. to 1000 c.c. daily. In Case III the volume was moderate and the specific gravity ranged from 1020 to 1030. In the remaining cases there were not enough observations to enable any general statements to be made as to the volume and specific gravity of the urine.

The nitrogen excretion was recorded in three instances, and it may be stated that it tends to be high in proportion to the weight of the child. For example, in Case II, with a weight of 32 pounds, the nitrogen excretion ranged from 5.7 grams to 6.5 grams daily. In Case I the nitrogen excretion ran uncommonly high, namely from 7 to 9 grams daily at a time when the weight was only 25 pounds. These

results are clearly attributable to the high protein feeding which was incidental to efforts to reduce the carbohydrates, which had proved very liable to cause diarrhoea. The excessive appetite was doubtless a factor in rendering it easy to consume so large an amount of protein food. The same statement may be made, though less strongly, in regard to Case II. In Case III the nitrogen excretion cannot be said to have run abnormally high in proportion to the weight of the child, though full data relating to this point are not available.

In regard to the nitrogen of ammonia in our cases, there is nothing noteworthy. In Case III the nitrogen of ammonia formed from 2.4 to 3.3 per cent. of the total nitrogen excreted. In Case II the nitrogen excretion was likewise normal, seldom going above 4 per cent. of the total nitrogen. In Case I also the nitrogen of ammonia usually varied within normal limits. A very large number of observations in this case show that the percentage of nitrogen of ammonia varied habitually between 3.25 and 4.50 per cent. At one time, while the patient had a cold in the head, the nitrogen of ammonia rose on two successive days to 4.78 and 5.96 per cent. of the total nitrogen. The urine at this time gave a strong Legal reaction for acetone in the distillate. On a few other occasions, however, the nitrogen of ammonia reached

or exceeded these figures without being associated with acetone.

As regards the excretion of uric acid in this case, it may be stated to have been so variable, as measured by the ratio between uric acid and the urea output, that no definite conclusions can be reached in the case of patients Nos. II and III. This is true also of Case I during the early period of observation, but during recent months (March and April, 1908), under conditions of great uniformity of diet and habits, the uric acid excretion (like that of total nitrogen) varied but little from day to day With a few exceptions the uric acid bore a proportion to the urea very close to 1:30. Taking into account the nature of the diet[1] this must be regarded as indicating an excessive excretion of uric acid, both absolute and relative.[2] It is worthy of notice that there should have occurred a rise both in the absolute and the relative amount of uric acid excreted just at the time when the nutritional conditions of the patient began to undergo a distinct improvement.

[1] Given in section on therapeutic measures.

[2] For example the actual quantities excreted during successive days is expressed in grams by the following figures: 0.383, 0.388, 0.413, 0.454, 0.397, 0.387, 0.439, 0.406, 0.421, 0.427, 0.399, 0.488, 0.458, 0.486, 0.452, 0.449, 0.477, 0.433, 0.443, 0.517, 0.463, 0.427, 0.432, 0.449, 0.459, 0.480, 0.471, 0.545, 0.452, 0.473, 0.461, 0.468, 0.466, 0.456, 0.406, 0.415, 0.467, 0.422, 0.420, 0.397, 0.437.

Special attention was devoted to a study of the urinary indications of putrefactive decomposition in the intestine. Such indications are known to have been very pronounced in Cases I, II, III and IV, and very similar indications of putrefaction have been found in the subacute infections of early infancy already alluded to as being associated with the Gram-positive fecal fields. The urinary signs of excessive decomposition in the intestine are shown mainly in four different ways: First, there is a rise in the ethereal sulphates. It is no uncommon thing in cases of infantilism for the ratio of the ethereal to the preformed sulphates to reach 1:4 or 1:6, whereas the normal ratio in childhood is 1:12 to 1:18. Even higher proportions are observed in the subacute stage which the writer regards as leading into the chronic state of infantilism. Secondly, pronounced indicanuria is a very prominent feature, as shown in all the cases examined except Case V, which did not come under close observation until the nutritional state had begun to improve. Quantitative determinations of the indican have not been made, but the qualitative results leave little doubt that the indican is habitually highly excessive when the disease is at its height. This is true also of the subacute fore-period of the disease. It is true, however, that with the improved intestinal con-

ditions which precede a change for the better in nutrition, the indican may begin to decline. There may thus be a time in the history of the disease when despite the fact that the child still remains nearly stationary in weight from week to week, and even from month to month, the indican is much lower than was previously the case. Another apparently regular feature of the putrefactive decompositions in infantilism is the occurrence of an excess of phenol in the distillate of the urine (the distillates include phenols and cresols). The observations made in our cases are partly quantitative by the method of Kossel and Penny and partly qualitative (with Millon's reagent). In Case II the repeated examinations of the distillate made at short intervals during a period of five years showed an excess of phenol to be a regular feature. The phenol for 24 hours varied from 38-90 milligrams (in the quantitative observations). Case III likewise gave very strong Millon reactions with the distillate. In Case I the distillate also regularly contained excessive amounts of phenolic substances as indicated by the following figures (representing milligrams) for the twenty-four hours: 75, 71, 84, 79, 87, 93, 62, 78, 90, 100, 74, 62, 87, 90, 73, 90, 45, 81, 91, 63, 74. Once without assignable cause the phenol in the distillate fell to 19 milligrams. Another feature

of the urine referable to putrefactive decomposition in the intestine is the presence of aromatic oxyacids in the urine. It is probable that both paraoxyphenylacetic acid and paraoxyphenylpropionic acid are frequently present in excess in these cases.[1] The acids in solution in the urine are capable of reacting with Millon's reagent even in the cold, and it is a noteworthy feature of our cases that in many instances the urine gives the characteristic behavior of the aromatic oxyacids when treated with Millon's reagent in the cold. Urines containing these aromatic oxyacids also give a marked diazo-reaction after distillation of the phenols. It may be mentioned further that the urines from the subacute infections, which are regarded as constituting the early stage of chronic infantilism, are liable to give a very pronounced reaction with Millon's reagent in the cold in the absence of volatile phenols. Finally it should not be overlooked that a marked degree of indolaceturia occurred in Case I and was a continuous feature in this patient. The presence of indolacetic acid was detectable also in the urine of Case II where, however, it was not pronounced. In Case III

[1] Paraoxyphenylacetic acid is not readily burned in the body and hence appears in the urine when absorbed from the intestine. The homologous higher acid undergoes combustion and hence is less likely to reach the urine, even if formed in equal or greater amount as the result of putrefaction.

it gave rise to a moderate reaction with strong hydrochloric acid and potassium nitrite. From experience gained with the urines of the subacute infections leading to chronic infantilism, I am disposed to think that indolaceturia is not a regular feature in this type of disease, although it is sometimes very prominent.

It may be further stated that the urines from the cases of infantilism showed slight or negative reactions with paradimethylamidobenzaldehyde, that skatol red was regularly absent and that in Cases I, II and III the urines were sometimes observed to show a slight reducing action when boiled with Fehling's solution.

Features Relating to the Intestinal Contents. There are several features relating to the gross and microscopical appearances of the intestinal contents and to their chemical nature which require at least brief consideration. The character of the movements is influenced to a considerable extent by the nature of the food, and in general it may be stated that on an ordinary mixed diet containing a fair proportion of fat, carbohydrates and proteins and in which milk forms part of the regimen, the movements are voluminous, gray or light-brown in color and of sufficiently low specific gravity to float on the surface of water. If the quantity of food be considerable the movements may

be very large indeed. If the carbohydrates be abundant, the fresh movements are apt to be filled with bubbles of gas. The stools are usualy formed, though so soft that any increase in the watery constituents gives the stool a diarrhoeal character. The movements usually have a sour odor which is clearly recognizable despite the fecal odor due to the presence of indol. The odor of butyric acid is seldom more than slight and is frequently absent. Mucus is very abundant at times both in masses on the surface of the feces and intimately mingled with them in small bits. In loose movements after the use of calomel large flakes of mucus are usually brought away. Large numbers of well-preserved individual epithelial elements are habitually carried away in the feces. Their number may be very large in some parts of the stool. Preparations of the feces show moderately dense bacterial fields almost always containing numerous epithelial elements, with nuclei usually well preserved and with a small area of cytoplasm about them. These epithelial elements may occur separated or closely aggregated in considerable numbers. In some cases it is common to find on the surface of the feces and mingled with the mucus, numbers of small, spheroidal cells, from three to four microns in diameter, containing spherical nuclei and pos-

sessing homogeneous, highly refractile cell bodies. They are often bile-stained, and if present in large numbers give a pink or reddish color to the mucus with which they are mixed. These cell elements stain readily with carbol-fuchsin and are acid-fast. When I first saw them I thought they might be epithelial elements, but now believe them to have an origin extraneous to the digestive tract. They may possibly be some form of yeast, but the fact that we have not been able to grow them in sugar media appears against this view.

The microscopical fields show the presence of an abundance of fatty acid crystals, and it is owing to the presence of these that watery suspensions of feces (say one gram feces to ten grams water) in a test tube show the optical peculiarities due to the presence of large numbers of small crystals. The reaction of the feces is usually slightly acid, but often it is neutral. If, however, meat be an abundant constituent of the diet the reaction may be slightly alkaline. In some instances it has been noticed that the drying of the feces is associated with the separation of large numbers of crystals which have the characteristic appearance of triple phosphates (ammoniomagnesian phosphate).

There are also several chemical characters in the feces of infantilism which deserve men-

tion. Even when the feces are acholic in appearance, extraction with alcohol shows the presence of moderate quantities of bilirubin. It is thus erroneous to draw the conclusion from the appearance of the stools that bile fails to enter the intestinal tract. It is also noteworthy that the reaction for hydrobilirubin with concentrated bichloride of mercury is extremely slight and sometimes negative. This points to the absence of a strong reducing action on the part of the bacteria present in the intestinal tract. I think it probable that the failure to detect marked evidence of reducing action by the bacteria in the digestive tract is to be explained in these cases by the comparatively small number of microörganisms of the butyric acid type—a type conspicuously active in causing reductions. Indol is a nearly constant constituent of the freshly voided feces in children suffering from intestinal infantilism. It may easily be demonstrated in the distillate either by the paradimethylamidobenzaldehyde reaction of Ehrlich, or better still, by means of the β-naphthaquinone sodium monosulphonate reaction. The quantity is usually not large, but rarely may run up to 20-30 milligrams in 100 grams of the moist feces. The presence of indol in the feces may be correlated with the occurrence of strong indicanuria, but sometimes the indicanuria may be

pronounced even though only a trace of indol is detectable in the feces. This is owing to the fact that there is not any fixed relation between the quantity of indol produced in the intestine and the quantity absorbed. As the patients improve in digestion and nutrition, the quantity of indol in the feces grows less, and may in time become very slight. In diarrhoeal movements also the proportion of indol is apt to be slight. I have never observed skatol in the movements from any patients of the type now under consideration. Phenolic substances can almost always be detected in slight amounts in the distillate from the feces. Sometimes the reaction for them is strong. In Case I the feces contained a substance which gave reactions corresponding to indolacetic acid. I have not, however, had the opportunity to separate this substance in purity and in sufficient quantity from the feces to actually settle its identity. The hydrogen sulphide contents of the feces in cases of intestinal infantilism is commonly small.[1]

[1] The following determinations of hydrogen sulphide in the feces are indicative of the range in percentage:

CASE I Date	Per cent. solids	Per cent. H_2S
Nov. 27, '07	25.89	.0144
Nov. 29, '07	9.97	.0144
Dec. 3, '07	29.85	.0113
Dec. 5, '07	25.41	.0127

The hydrogen sulphide exists in bound form, and I have never been able to detect the free gas in the fresh movements. Methyl mercaptan is also absent although the bacteria from the feces may produce a small amount of methyl mercaptan when grown in plain broth. It appears true in general, however, that the bacteria present in these cases do not form mercaptan abundantly, and commonly they do not make it at all under the conditions just mentioned. The volatile fatty acids derivable from the feces in cases of infantilism are moderate in amount and appear to be rather low in butyric acid. Acetic acid may be detectable. Aldehydes have not been detected. The gas production of the mixed fecal flora when grown in dextrose, saccharose and lactose bouillon, is variable. Commonly it is smaller than normal. The fecal flora may, indeed, fail to form gas under these conditions. With

Date	Per cent. solids	Per cent. H_2S
Dec. 7, '07	17.37	.041
Dec. 7, '07	32.60	.031
Dec. 10, '07	27.67	
Dec. 11, '07	28.82	.0111
Dec. 14, '07	28.04	
Dec. 16, '07	27.00	.0190
Dec. 20, '07	20.88	.0170
Dec. 24, '07	26.15	.0201
Jan 18, '08	21.00	.009

These low percentages of hydrogen sulphide are the more noteworthy in view of the excess of other putrefactive products.

improvement attended by a return of *B. coli* and *B. lactis aerogenes* the gas production increases to normal.

The Calcium and Magnesium Balances. In the state of arrested development which constitutes the striking feature of the cases of infantilism here reported, it is of especial interest to seek for information regarding the calcium and magnesium intake and output. It is obvious that the failure of skeletal growth calls for explanation and that this explanation is to be sought either in the inability of the skeleton to utilize calcium and magnesium coming to it in the blood, or the inability of the blood and lymph streams to obtain from the digestive tract sufficient quantities of the alkali earths to supply the necessary materials for skeletal growth. In order to determine the relations between the intake and the outgo of the alkali earths from the body in a state of infantilism, two observations were made by Dr. Wakeman upon Case I, each observation covering a period of ten days. The second of these observations serves as the basis for the data to be referred to here, the observation having been made under thoroughly satisfactory conditions from every point of view. The period of ten days in question extended from noon, March 10, 1908, to noon, March 20, 1908 —a period during which the subject remained

essentially stationary in weight. The calcium, magnesium and phosphoric acids taken in the food were accurately determined. The calcium, magnesium and phosphoric acids were also determined in the urine and feces corresponding to this period, the feces being carefully marked off from the fore and after periods by means of charcoal.

During the period of ten days the calcium (calculated as calcium oxide) found in the urine was 0.1151 grams, giving a daily average of 0.0115 grams. In the feces during the same period, the calcium oxide amounted to 9.59 grams, giving a daily average of 0.959 grams. The calcium oxide present in the feces and urine together during the ten days amounted to 9.71 grams, with a daily average of 0.971 grams. The calcium oxide of the food during the same period amounted to 9.81 grams with a daily average of 0.982 grams. There was thus a positive balance of calcium during the ten-day period amounting to 100 milligrams, indicating a daily retention of calcium oxide of only 10 milligrams. It is roughly estimated that in the normal growth of a child between the second and the sixteenth years, the daily retention of calcium oxide by the body should be more than ten times the amount retained in this case. The amount indicated as retained is, in fact, so small in this instance as to fall

almost within the limit of experimental error. There was thus no appreciable retention of calcium oxide during the period in question. During another ten-day period in which the calcium oxide was studied by Dr. Wakeman under somewhat less favorable experimental conditions, there was shown an actual loss of calcium oxide in the feces and urine as compared with the calcium oxide taken in with the food. The very small quantities of calcium found in the urine in the experimental periods relating to this case point to defective absorption of calcium from the intestinal tract.

Precisely similar results were obtained from the study of the magnesium balance. During the ten-day period corresponding to the one for which the figures for calcium oxide have just been given, the urine contained one gram of magnesium (calculated as magnesium oxide), giving an average of 0.10 grams daily. During the same period the magnesium in the feces was equivalent to 1.35 grams of magnesium oxide, giving an average of 0.135 grams daily. The magnesium oxide of the urine and the feces in this ten-day period was equivalent to 2.35 grams. On the other hand, the magnesium of the food (calculated as magnesium oxide) was 2.19 grams. It is thus evident that for the entire period of ten days there was a loss of magnesium oxide equivalent to

0.16 grams. This amount may possibly fall within the limits of experimental error. The result indicates that during the period in question the body was retaining no magnesium. The cause of this failure of the organism to retain magnesium and calcium will be discussed in considering the pathology of infantilism.

The study of the phosphoric acid of the urine and feces on the one hand, and of the food on the other, gives results comparable with those just given for calcium and magnesium. During the ten-day period the urine contained 10.46 grams of phosphoric acid, or an average of 1.05 grams of phosphoric acid daily. The feces during the same period contained 10.70 grams of phosphoric acid, an average of 1.07 grams daily. During the ten-day period the urine and feces together contained 21.16 grams of phosphoric acid with a daily average of 2.12 grams. During this same time the food contained 20.29 grams of phosphoric acid with a daily average of 2.03 grams. These results thus indicate a slight loss of phosphoric acid during the ten-day period in question, but the loss is so small as to fall nearly within the limits of experimental error, and hence is to be disregarded.

The Fat Loss by the Feces. In all of the cases of infantilism it has been noteworthy that the stools have been excessively fatty,

even where only moderate quantities of fat have been taken with the food. The presence of large amounts of fatty acids has already been referred to in speaking of the appearances of the feces in these cases. Another characteristic is the presence of soaps, the white masses of which, looking like small granular coagula of casein, sometimes give a very noteworthy appearance to the stools. These masses of white soaps (probably calcium soaps) have often been mistaken for casein.

In Case I the fats of the feces were subjected to careful study. It was found that the total percentage of fats in the solids was uniformly high even on a diet containing only moderate amounts of fat. Thus at different periods, lasting from two to ten days, the percentages of fats of the solids of the feces amounted to 29.80, 31.93, 32.78, 44.60, 39.21, 41.96, 47.26, 40.90, 25.01, 39.66, 36.16. These figures include not merely the ethereal extracts, but also the fatty acids in the form of soaps. They therefore represent the total fats lost. It will be seen that these figures represent a large loss of fat of the food. The actual loss of fat for various periods is shown by the following table, which shows also the losses of soaps and the losses of calcium combined as soaps (assuming the soaps to consist wholly of soaps of calcium):

TABLE I

Showing actual loss of fat with feces during various periods: CASE I

Date of Period	Total fats per period Grams	Soaps per period Grams	Calcium Oxide from soaps per period Grams
Dec. 2, 6, 8, '07.....	21.6	1.46	0.145
Dec. 13, 14, 19, 20, '07..	23.8	0.93	0.092
Dec. 20, 21, '07.....	22.2	3.16	0.313
Dec. 25, 29, 31, '07.....	20.9	2.69	0.266
Jan. 19, 20, '08.....	13.0	2.61	0.258
Jan. 26, 27, '08.....	17.0	4.20	0.416
Feb. 8, 9, 10, '08.....	29.2	4.67	0.463
Feb. 14, 15, 16, 17, '08..	32.1	4.74	0.469
March 10 to 20, '08....	55.6	10.80	1.070

Comparing these figures, representing the loss of fat, with the figures representing the intake of fat during one of the periods studied (March 10-20, 1908) it was found that the percentage of fat absorbed was 85.5, while the percentage of fat lost was 14.5. These figures indicate the considerable extent to which the fat is lost in these cases on a diet containing only a moderate amount of fat, since in a normal individual one would look for a fat absorption of from 92 to 98 per cent. But these figures relate to a period of improvement and by no means show the worst fat absorption noted in Case I. At an earlier period, with the same daily intake of fat (38.28 grams), the losses were frequently from 20 to 25 per cent., and once reached 40 per cent. of the ingested fat.

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Observations have been made in Case I relative to the proportions existing between the neutral fats, the fatty acids and the soaps. They show that fat splitting and saponification have occurred in high degree in the intestinal tract, since the fatty acids range from 40.75 per cent. to 80.25 per cent., while the soaps vary from 3.89 per cent. to 20.08 per cent. The neutral fats, on the other hand, range from 6.88 to 39.85 per cent. It is thus evident that the greater part of the fats lost are in the form of fatty acids and that the sum of the fatty acids and the soaps make up on the average about three quarters of the total fat lost. These losses cannot, of course, be attributed to any failure of fat splitting in the intestine, but are clearly referable to a diminished power of absorption. It is noteworthy that so considerable a percentage of the total fats lost is in the form of soaps of the fatty acids. The importance of this fact lies in the consideration that these soaps are for the most part calcium and magnesium soaps (chiefly the former), and that they represent a loss of calcium and magnesium to the organism dependent on non-absorption of the soaps of these alkaline earths. It is true that only a relatively small percentage (say 10 per cent.) of the calcium lost in the feces is present in the form of soaps, but it

is obvious that the non-absorption of the quantity of calcium represented by this proportion is enough to determine whether the organism shall or shall not gain calcium for the purpose of building up the skeleton. The same considerations hold true also of magnesium.

Let us take a specific example relating to calcium. Between March 10 and 20 there was a loss of 10.8 grams of soaps. These soaps consist almost entirely of soaps of calcium and have been calculated as such in the foregoing table. On this assumption the calcium oxide representing these soaps would amount to 1.07 grams. For a period of one year the calcium oxide thus lost as soaps would amount to more than 36 grams. The gain of so much calcium by the skeleton, or its loss through the feces, is clearly an important element in the skeletal growth.[1]

[1] I have calculated that the average yearly accretion of calcium oxide by the skeleton between the third and sixteenth year is 51.6 grams. If we deduct 36 grams of calcium oxide as representing the loss through soaps, we see that there will be left but little calcium for the purpose of skeleton building.

The above result was reached by the following data:

Estimate of the average yearly addition of calcium (as calcium oxide) to the human skeleton between the third and sixteenth year.

Weight of body at 3 years	16 kilos
Weight of body at 16 years	50 kilos
Estimated weight of skeleton in % of total at 3 years	15%
Estimated weight of skeleton in % of total at 16 years	17%
Weight of skeleton at 3 years	2.4 kilos
Weight of skeleton at 16 years	8.5 kilos

Pathology

It is desirable to consider the data that have been presented in the foregoing pages with a view to their bearing on the pathology of intestinal infantilism. It is believed that the data now available suffice to form a conception of the nature of the processes that underlie this serious disorder of nutrition, even if they do not serve to satisfactorily clear up all questions relating to the etiology of the affection. There are two large and distinct but related features of intestinal infantilism which must be taken into account in any endeavor to understand the morbid processes on which the clinical manifestations depend. These are, first, the extreme retardation in general bodily development, secondly, the state

Undried bone contains 22% of bone earth
Skeleton of 2.4 kilos contains 0.53 kilo bone earth
Skeleton of 8.5 kilos contains 1.87 kilos bone earth
Accretion of bone earth by skeleton between the age of 3 and 16 years equals 1.34 kilos
Bone earth contains approximately 84% calcium phosphate
Bone earth contains approximately 13% calcium carbonate
1.34 kilos bone earth contain 1.125 kilos calcium phosphate
1.34 kilos bone earth contain 0.175 kilos calcium carbonate
1.125 kilos calcium phosphate contain 0.60 kilos calcium oxide
0.175 kilo calcium carbonate contains 0.07 kilos calcium oxide
Total calcium oxide in 1.34 kilos of bone earth = 0.67 kilos calcium oxide

This represents the accretion of calcium oxide during thirteen years of skeletal growth. The yearly average accretion of calcium oxide in skeletal growth between these years therefore equals 0.0516 kilos or 51.6 grams.

of intoxication which manifests itself in prominent derangements of the neuromuscular system.

The Retardation in Development. The retardation in the development of the body implicates, as already stated, the skeleton, muscles, fat and viscera generally, while slowing the growth of the brain in relatively slight degree. Where are we to seek for an explanation of the actual check to the general growth and the disparity in state of bodily nutrition as compared with that of the brain?

The retardation in growth undoubtedly depends in the main on a simple cause—insufficiency of the foodstuffs absorbed from the digestive tract. Such insufficiency of absorption may be referable to an inadequate food supply or to imperfect absorption of foodstuffs from the tract. The dietetic conditions in our cases were of such a nature as not to exclude the former factor, although making impaired absorption largely responsible for the diminished supply of food materials available for the growth of the body. In thus stating the case no allowance is made for the possibility that there may be disturbances of metabolism which make for the impaired utilization of foodstuffs after their absorption. It will be pointed out in the course of this discussion that metabolic derangements do to some extent exist, but that they are to be con-

sidered as secondary to the absorption of mildly toxic but continually formed products. The following considerations will, I believe, serve to show that the leading cause of the arrest of growth is neither deficient food[1] nor specific disorders of metabolism, but serious defects in digestion and absorption which find expression in a failure of the organism to get its proper share of nutritious materials from the digestive tube. These defects may be considered from the standpoint of the carbohydrates, the fats, the proteins and the salts respectively.

It has been pointed out that a prominent feature in the nutritional history of intestinal infantilism is the intolerance for carbohydrates, which even in moderate amounts lead quickly to soft or diarrhoeal movements, often with an increase in mucus and sometimes with a markedly excessive formation of intestinal gases. Even if the disturbances incidental to the moderate use of carbohydrates are for a time at least less obtrusive than those just mentioned, the physician is ultimately convinced that his patient is freest from intestinal symptoms when this class of foodstuffs is much

[1] It is true that in each of the five cases there were times when the food was deficient in amount, but in all instances repeated efforts were made (sometimes unsuccessfully) to increase the food supply sufficiently to make it enough for the needs of normal children of corresponding weight, or even in excess of their needs.

restricted. This conviction has the practical result that the child is in considerable degree deprived of that class of foodstuffs on which the organism mainly depends for its caloric needs. The formation of adipose deposits depends in childhood, in at least a measure, on the ability of the organism to appropriate carbohydrates in greater quantity than is necessary to maintain the body weight, this surplus being clearly convertible into fat by obscure synthetic processes. Under normal conditions it is further probable that the sugars and starches furnish a portion of the material used in the upbuild of the living protoplasm generally, especially that of the muscles and parenchymatous organs. But from experience with diabetic persons and from various physiological facts we know that these functions of the carbohydrates may be in large degree substituted by the fats and proteins of the food. The development of a diabetic child is possible if the carbohydrates are replaceable by these other foodstuffs, but only in this case. The same statement probably holds equally true of many children suffering from digestive derangements. It being necessary to deprive our patients with infantilism to a considerable extent of their carbohydrates, we turn with especial interest to learn how these children dispose of their fats and proteins.

The fats are on the whole better tolerated than the carbohydrates by our patients with intestinal infantilism. That is to say, if we give to a child whose caloric needs are 1000 calories per diem, 100 grams of carbohydrates or its approximate caloric equivalent in fats (say 50 grams of fat), the latter may cause less obvious disturbances of function than the former. But from this we are not justified in concluding that the fats are in reality well utilized. They may be tolerated in the sense that they do not promptly bring on obtrusive symptoms, but examination of the movements shows that the absorption of fats is far below the standard for health, as regards neutral fats, fatty acids and soaps. Thus in Case I there was during a period of two days of fat diarrhoea a loss of 22.2 grams of fat (neutral fat, fatty acids and soaps) or 11.1 grams daily. This large loss in fat represents nearly 40 per cent. of the fat intake at the time and is equivalent to a waste of about 100 calories daily. Losses of from seven to eight grams of fat daily were common, representing 25 per cent. of the fat ingested. In this great loss of fat we have the key to the understanding of the failure in nutrition which constitutes the most prominent feature of intestinal infantilism.

It is obvious that such a fat loss (and the example is representative of the cases which have up to the present come to my notice, having been also marked in Cases II, III and IV), when added to an intolerance for carbohydrates, can lead to nothing less than a state of well-defined under-nutrition. We can imitate this condition by withholding fats in large degree from young animals. In making this experiment with young puppies and with young pigs I found it easy to prevent any increase in weight notwithstanding milk proteins were given much in excess of ordinary requirements, together with the milk sugar naturally present in milk. I therefore believe that the incapacity to absorb fats and carbohydrates is in itself sufficient to explain a state of infantilism in the human subject despite the free use of proteins. It will be seen, however, that the failure to absorb fats entails two other consequences which lend their influence to hinder development—a loss in calcium and magnesium salts and an increase in intestinal putrefaction. Before discussing these factors in the pathology of infantilism, it is desirable to consider the fate of the ingested proteins.

A study of the nitrogen balances (for three separate periods) derived from a comparison of the nitrogen ingested with the nitrogen lost with the urine and feces (in Case I) shows

that only an insignificant amount of nitrogen (0.65 gm. in 10 days) was retained. This is, of course, a not surprising result if we consider the very small gain of the patient in weight; and there is no reason to doubt that this result, derived from a study of Case I, could have been paralleled by studies of the nitrogen balances in any of the other cases of infantilism during the period of almost total arrest in growth.

TABLE II

Showing the intake of nitrogen with the food and loss of nitrogen with the feces, according to periods.

CASE I

	N of Food Grams	N of Feces Grams	Loss of N Per cent.
Period I (3 days).....	22.89	2.34	10.2
Period II (4 days).....	29.03	4.39	14.7
Period III (10 days).....	66.46	8.44	12.5

	Total N in Urine Grams	Total N in Urine + Feces Grams	Gain or loss in N per period Grams	Average daily gain or loss in N Grams
Period I (3 days)...	19.07	21.41	+1.48	+0.49
Period II (4 days)..	24.66	29.05	—0.02	—0.005
Period III (10 days)	56.36	64.80	+1.66	+0.166

If we look at the figures in Table II which relate to the absorption of nitrogen from the digestive tract, for the periods in question in Case I, we note that the absorption of protein (as measured by its nitrogen content) is not so complete as it should be. In period I, covering three days, the nitrogen of the food was 22.89 grams and that of the feces 2.34 grams. The loss of nitrogen by the feces in this period

was 10.2 per cent. In period II, covering four days, the nitrogen of the food was 29.03 grams, the nitrogen of the feces, 4.39 grams. The nitrogen lost by the feces in this period was 14.7 per cent. In period III the food contained 66.46 grams of nitrogen and the feces 8.44 grams. Here the loss in nitrogen equaled 12.5 per cent.[1] In health the loss of nitrogen by the feces under comparable conditions of protein feeding is not greater than 7 or 8 per cent. of the nitrogen ingested. So we may say that the protein absorption in Case I was somewhat under 90 per cent. instead of 92 per cent. or over. Protein absorption is therefore relatively much better than the absorption of fat, despite the fact that it is somewhat impaired.

Our interest in the fate of the inorganic salts centers about the alkali earths. It has been made out that in Case I, where a careful balance was made of the calcium and magnesium, the organism failed to gain either of these elements. Under these conditions it is not surprising that the skeleton should remain stationary in weight. In a healthy, growing child, weighing 25 pounds, there should be definite evidence of the absorption of calcium

[1] Some portion of the nitrogen of the feces is attributable to the epithelial detritus present here in excess, but it is difficult to make a fair allowance for this.

and magnesium in quantities sufficient to account for the uninterrupted and rapid growth of the skeleton during infancy and childhood.

Even under wholly normal conditions the quantity of calcium daily absorbed from the intestine of a young child is small, while the loss of calcium by the feces is large. Thus in a normal child of nine months the feces contained 2.122 grams of calcium (estimated as oxide), while the food contained only a little more than this—2.194 grams.[1] It is perfectly obvious that any influence which tends to diminish the absorption of this small proportion of the ingested calcium must jeopardize the small daily supply of this element which is required for the growth of the skeleton. And it is important to note that in some apparently healthy children the maintenance of a positive or negative calcium balance is determined by apparently so slight a factor as the variation in the percentage of fat in the milk. Thus Rothberg[2] found that the use of skimmed milk insured a positive calcium balance (even in some children with definite signs of rickets), whereas in a certain number of children the use of full-fat milk caused a

[1] See O. Rothberg. "Ueber den Einfluss der organischen Nahrungskomponenten auf den Kalkumsaltz kunstlich genahrten Saulinge." *Jahrb. f. Kinderheilk.*, 66, der dritten Folge, 16 Band, Heft 1, 1907.

[2] Loc. cit.

marked negative balance. Quite similar results were obtained by Birk[3] in his study of the magnesium metabolism in nurslings. And it may be further noted that both in the case of calcium and magnesium a negative balance may be induced in some children by the free use of carbohydrates, for reasons at present not clear.

It has been several times mentioned that a leading feature in the pathology of infantilism is the large loss in fat by the feces. A portion of this fat (varying in Case I from 14 to 20 per cent. of the total fat lost) is present as soaps and especially as soaps of calcium. If we assume that the soaps of the feces exist as soaps of calcium (an assumption not far from the truth, since magnesium soaps are present in only small proportion) it is clear that the loss of saponified fat entails a significant loss of calcium. Thus in Case I the loss in soaps during a ten-day period amounted to 19.8 grams, corresponding to a withdrawal of 1.07 grams of calcium oxide during the same time. This is a quantity of calcium sufficiently large to be of the first importance to the skeleton, for in a case where there is practically no gain and no loss in skeletal calcium, a positive balance would be established by the absorption and appropriation

[3] "Ueber den Magnesiumsaltz des Saulings." *Jahrb. f. Kinderheilk.*, 66 der dritten Folge, 16 Band, Heft 3, 1907.

of any portion of the calcium habitually lost as soap. The utilization of the entire amount of calcium present as soap would make possible a fair skeletal growth; and I have calculated that the full absorption of this calcium (through improved soap absorption) would in itself be almost enough to account for a wholly normal skeletal development. It is possible, however, that in order to secure normal skeletal growth we should have to obtain a somewhat improved absorption of calcium not present as soap. I cannot further discuss this point for I do not know enough of the conditions attending physiological fat absorption.

Sufficient evidence has now been brought forward to support the contention that the arrested growth of infantilism can be explained by the inability of the organism to secure an adequate supply of nutrient materials from the lumen of the digestive tract. The failure to absorb sufficient calcium and magnesium accounts for the arrest of skeletal growth; the restricted absorption of carbohydrates and fats explains the failure to lay up fat, and at least partially accounts for the cessation in the growth of muscle. The proportionate retardation in the growth of the viscera doubtless has a similar origin although possibly here the physiological adaptation of visceral structures to the needs of the rest of the body may have an influence. The relatively large

size of the head and brain may be in part due to the large size of the brain at birth, but it appears that the growth of the brain in infantilism is somewhat out of proportion to the very slow development or entire arrest of the body in general. This is perhaps attributable to the protected position of the central nervous system, in the sense that it not merely exercises a kind of first call on the nutritive materials which it requires but is also in large measure screened from the action of certain poisonous substances by the action of the liver, muscles, etc.

The leading feature of infantilism—the prolonged arrest of development in early childhood—is thus seen to be due to an impaired power of absorption of nutrient materials in so far as it depends on a lack of available fats, salts and proteins. The relation between insufficient carbohydrates and defective absorption is less simple, for the restriction in this class of foodstuffs is often one encouraged by the physician on account of the evil consequences following even the moderate use of sugars and starches. Probably a failure on the part of the intestine to promptly absorb the dextrose formed during the digestion of starches is a factor in depriving the organism of its proper share of carbohydrates, but this would perhaps not suffice to make this deprivation significant but for the

intervention of a second factor, namely the excessively rapid decomposition of dextrose by bacteria.

The impaired power of absorbing foodstuffs from the intestinal tract I believe to be referable to a chronic inflammatory process implicating especially the lower lengths of the small intestine and perhaps the contiguous portion of the colon. This inference is based in part on the occurrence of mucus and epithelial cells intimately mingled with the intestinal contents and partly on certain resemblances between the signs of chronic saccharo-butyric putrefaction in adults, a condition in which there is direct evidence of congestion and inflammation of the mucous membrane of the ileum and colon. The inflammation of the digestive tract in infantilism can be confidently attributed to the presence and dominance of an unsuitable bacterial flora.

It is likewise to this unsuitable bacterial flora that we have to attribute the excessive putrefactive decompositions in the intestinal tract on which depends the second leading group of symptoms of intestinal infantilism—namely the chronic intoxication of the neuromuscular system which is in every case discernible. Among the products of putrefaction in the intestine are indol, indolacetic acid, phenol and the aromatic oxyacids. We know that indol exerts

an irritant action on the central nervous system, an action which if long continued leads to depression of function. Likewise the depressant action of indol on the muscles is well marked.[1] Of the action of the other aromatic putrefactive substances on the neuromuscular system little is positively known. Clinical observation makes me think that indolacetic acid may exert an action similar to that of indol, but milder in intensity. The fact that the signs of intoxication (emotional irritability and depression, rapid muscle fatigue) undergo striking amelioration coincidentally with a marked fall in the quantity of the aromatic putrefactive substances in the urine seems a reliable indication that the neuromuscular intoxication is related to the excessive absorption of such putrefactive substances from the digestive tract. There is another aspect of this excessive putrefaction which must not be overlooked in any discussion of the pathology of infantilism, namely the loss of food material which it entails. As an instance we may take the case of tryptophan and indolacetic acid. The latter is sometimes formed in such large quantities from the former, in the course of putrefaction, as to rob the organism of a not insignificant quantity of tryptophan—an amino-acid which

[1] See experiments of F. S. Lee, mentioned in my volume, *Common Bacterial Infections of the Digestive Tract*, p. 255.

there is every reason to regard as essential to nutrition. There may be a similar loss of tyrosin owing to the putrefactive conversion of this amino-acid into aromatic oxyacids in the intestinal tract. Finally it must be regarded as an open question whether the products of putrefaction, after absorption, may not have some damaging influence on the processes of metabolism themselves through their action on cells entrusted with important assimilative powers.

The two cardinal features of infantilism, arrest of bodily growth and the group of symptoms based on chronic intoxication, thus have their origin in an abnormal intestinal flora possessed of a high degree of parasitism owing to a long period of adaptation. The nature of the pathological flora has been already described in so far as it has been studied in a small number of typical examples of intestinal infantilism. The interpretation of these findings can, however, be undertaken only with much caution, owing to the scantiness of our real knowledge of the biological characters of the microörganisms which we have found to be so regularly and persistently associated with intestinal infantilism. The evidence on which we must base a judgment is circumstantial rather than direct. It is unlikely that the pathological state can be experimentally repro-

duced in animals by means of the organisms which we have found to be characteristic of the chronic human infection. The ordinary tests of pathogenicity have given negative results with the three types of organisms which appear most intimately related to the infection, namely *B. bifidus, B. infantilis* and the cocco-bacillary forms.[1] In other words, we cannot here apply the criteria that have served so well in studying acute infectious diseases. There are, nevertheless, certain obtrusive phenomena which cannot be overlooked and which call for some comment. The great abundance of *B. bifidus* in the formed and diarrhoeal stools of infantilism, and in the mucus contiguous to the mucosa, suggests a relationship of a causative nature to the inflammatory process within the gut. This suggestion is made the more reasonable by the fact that periods of improvement in absorption (due presumably to amelioration in the intensity of the inflammation) have been associated in numerous instances with a partial disappearance of *B. bifidus* from the stools or through a modification in the morphology of the organism pointing plainly to a decline in vigor. It is perhaps true that the same argument might

[1] It should be stated that a dog was fed on milk inoculated with *B. infantilis* after sterilization. The animal developed a persistent diarrhoea which ceased only with the discontinuation of the infantilis milk. A second trial gave a similar result.

be applied with equally good reason to the relation of *B. infantilis* to infantilism, except that we have not found this organism in the mucus. Finally the fact must be mentioned that the disappearance of *B. bifidus* and *B. infantilis* has been noticed to be concomitant, not only with clinical improvement, but with an increase in the numbers of the cocco-bacillary forms which are apparently always present. This fact seems to indicate that this group of organisms is less objectionable than the micro-organisms which it replaces. A fact which calls for especial comment is the occurrence of *B. bifidus* and *B. infantilis* in the stools of normal infants and in small numbers in some healthy adults. Tissier and other French observers have insisted on the presence of *B. bifidus* in the stools of nurslings, even maintaining that this microörganism is the characteristic and dominant one. It is necessary to reconcile this contention with the suspicion just expressed that *B. bifidus* is actually an injurious agent in our cases of infantilism. In this connection it is important to state at the outset that the study of many Gram-stained smears from normal nurslings indicates that in the United States there are numerous normal nurslings from whom one can obtain no evidence of the presence of *B. bifidus* in the stools; and this assertion is supported by

the results of careful cultural procedures carried on by experienced persons. On the other hand, *B. bifidus* did appear in the cultures from some of the normal nurslings' stools examined by us; and in some instances the Gram-stained fecal fields showed a great abundance of positive forms possessing a morphology indistinguishable from the plain form of *B. bifidus*. But there are two comments to be made on these findings. First, we have never been able to obtain in plate cultures so many bifidus organisms from normal nurslings as from cases of infantilism, and it seems a safe inference that these bacteria are in reality more abundantly present (in at least some cases of infantilism) than in healthy nurslings. Secondly, it must be plainly stated that there is no sound evidence that the greater number of the Gram-stained positive bifidus-like bacteria in the nurslings' stools are in reality examples of *B. bifidus*. The French writers have assumed that the organisms seen in the fecal fields are bifidus, but the contention has never, I believe, been successfully sustained by adequate cultural methods. We know that *B. infantilis* and some acidophile bacteria (other than *B. bifidus*, which is to be ranked as an acidophile microörganism in the sense of being able to grow in a strongly acid medium, though not in the sense of being restricted in

growth in a neutral medium) may exist in fecal fields side by side with the plain form of *B. bifidus* and indistinguishable from it.

Thus such evidence as is now available indicates that *B. bifidus* is considerably more abundant in the stools of infantilism than in the stools of normal nurslings. It may be that any detrimental action exerted by these bacteria is due to their relative predominance in the intestinal tract of infantilism, perhaps also to a failure in a normally existing balance or symbiosis with bacteria of the *B. coli* or *B. lactis aerogenes* types. It will require considerable further study to determine this question. Likewise the relation of *B. infantilis* to the genesis of infantilism must be left open. It may, however, be stated with much confidence that intestinal infantilism is associated (at least in some of the most extreme cases) with the persitence and dominance of types of flora which belong especially to the period of infancy and the persistent dominance of which in the third, fourth, fifth, sixth and even eighth year of life (as I have observed it) must be regarded as distinctly pathological.

There are some features in the pathology of infantilism that remain obscure despite a somewhat close study of the subject. For example, I cannot yet offer a satisfactory explanation of the extreme abdominal disten-

sion met with in most of our cases. Neither *B. bifidus* nor *B. infantilis* are gas-formers. The same is true of the various coccal and cocco-bacillary forms. It is unlikely that any of them are primarily concerned with the intestinal gas-production. Possibly owing to slow absorption from the small intestine the carbohydrates there are decomposed by *B. lactis aerogenes,* which is probably present in the upper part of the small intestine. We know, for example, that when acting on potato this organism forms gas abundantly. But the study of the diarrhoeal fecal fields gives no suggestion that there is any excessive multiplication of *B. lactis aerogenes* in the small intestine.[1]

I find it impossible at present to offer a well-supported explanation of the putrefactive cleavages which are so active in the intestine. Which bacteria or groups of bacteria are responsible in this disease for the production of indol, indolacetic acid, phenol and para-oxyphenylacetic acid is still far from clear. Until we meet with more success in getting *B. infantilis* and *B. bifidus* to grow outside the body as they grow in the intestinal tract, we cannot hope to clear up this feature of

[1] It must be remembered that we have not had the opportunity to study bacteriologically any of our infantilism patients in the stage characterized by active gas-formation and distension of the small intestine.

the pathology of the affection, and it seems best at present not to attempt its discussion.

It has been shown that the persistence and overgrowth of bacterial flora of the nursling period is a characteristic of the infantilism patients reported in this publication. Of the conditions leading to this persistence and overgrowth nothing positive is known, and this necessary knowledge can be gained only by very careful and extended bacteriological studies of the intestinal bacteria in the earliest stages of the disease.

The condition of infantilism which has been described is one possessing clearly defined clinical characters. Whether the bacterial causes of the affection, or, more properly, its bacterial associations, are always of the same nature as those here described must be left an open question. The studies which have been made point to a definite relation between the clinical phenomena and the peculiar bacterial flora, but the thoroughly studied cases have been few, and wider experience may possibly teach us that our definite clinical type may be associated with more than one group or symbiotic association of bacteria.

Other etiological factors than intestinal infection in the cases of intestinal infantilism seem improbable, although they cannot be positively excluded. The recovery which has taken

place in Case I, and in a still more striking degree in Case II, as a result of carefully planned dietetic and hygienic measures, seems to speak against the specific influence of non-intestinal elements of causation, as for example disorders in the functions of glandular organs, such as the thyroid gland or the anterior lobe of the pituitary body. It is noteworthy that in all our cases of infantilism there have been at least some indications of rickets. Since the retardation in the growth of the skeleton seems clearly referable to the inadequate absorption of calcium and magnesium, it is likely that such indications of rickets as have been observed are also related to this defect in assimilation of the alkali earths. Our cases point, however, to the correctness of the view that something more than mere failure to adequately absorb calcium and magnesium must enter into the pathology of rickets, since in cases of such marked skeletal retardation as we have in our examples of infantilism there should have been the fullest opportunity for the development of rickets, were this disease dependent merely on the non-assimilation of the bone-forming elements. Under the circumstances the relative slightness of the rachitic manifestations is a feature of considerable interest.

The Acute and Subacute Infections Leading to Infantilism

Although unable to give an adequate account of the bacteriology of the acute and subacute cases of enterocolitis which in my judgment are the antecedents of chronic infantilism, I wish to mention here the existence of a type of intestinal inflammation which stands in this causative relation to the chronic affection. These cases usually begin between the end of the first year and the middle of the third. They are characterized by diarrhoea (usually without tenesmus) with an abundance of mucus, but no blood. The diarrhoeal discharges are usually not very frequent. The loss in weight is not rapid (1-2 ounces daily), but may progress until the child is much emaciated. There is usually considerable flatulence. There is a moderate or marked fall in haemoglobin. The temperature is normal or subnormal. The appetite may be unimpaired. The disease lasts from three to six weeks and recurrences are very apt to occur. The carbohydrates are very badly tolerated and many relapses are certainly due to their incautious use.

The urine in the course of this disease gives intense reactions for indican and for aromatic oxyacids.

An examination of the Gram-stained fields from the stool of a typical example of this

infection shows it to consist almost wholly of Gram-positive bacilli (often lying parallel to each other in groups) presenting the morphological characters of the simple form of *B. bifidus*. From the stools *B. bifidus* can be readily cultivated and the same microörganism grows very freely in its bifid forms in dextrose bouillon fermentation tubes. *B. infantilis* is obtainable from the stools of some cases, perhaps of all. From the mucus *B. bifidus* grows freely, sometimes almost alone, in fermentation tubes. It appears probable that *B. bifidus* is very abundant in the stools of these cases, but it is not possible at present to say to what extent it makes up the fecal fields. A noteworthy feature is the very small number of Gram-negative bacteria seen in the fields.

The close similarity between the intestinal flora in this acute or subacute affection and in infantilism makes a causal relation between the former and the latter highly probable. Up to the present time I have had no opportunity to observe an indubitable transition of the acute disease into the chronic one with the help of methods adequate to establish the proof of such a relation as that just suggested. The methods now employed were not known to us when the cases of infantilism here described were in their subacute stage. On the other hand, the acute or subacute cases presenting

the flora above mentioned have not been long enough under observation to determine whether any of them are developing the extreme and persistent retardation to which the word infantilism may properly be applied.

Mild Types of Intestinal Infantilism

It seems to me desirable to restrict the use of the word infantilism to those cases of intestinal origin in which the subjects are strikingly undeveloped for years and in which the absolute arrest of growth has persisted for at least one year. The atrophic conditions of infancy which are grouped under the term marasmus belong in a different clinical category and have, I believe, a different genesis. There are, however, instances of a moderate retardation in growth (not necessarily with actual arrest in development) which appear to be mild types of the condition which has been described in this study only in its extreme examples. *B. bifidus* appears to be less abundantly present in these milder cases, in which various coccal forms may be prominent and in which Gram-negative forms (representing *B. coli*) are probably seldom lacking. No serious attempt has yet been made to study these mild forms of arrested growth of intestinal origin, but there is reason to think that at least some of

these cases are allied to the severer type both in etiology and pathology.

The Sequelae and Prognosis of Intestinal Infantilism

I have not at command the data from a sufficient number of instances of infantilism to permit even an approach to generalization as to the outcome of the disease. Only the patient study of many cases through extended periods of time and under well understood conditions will yield the facts necessary for safe generalization. Nevertheless there are some obvious commentaries which are justified by limited experience. Of these by far the most important is that in general the outlook is very largely determined by the nature of the care which the patient can obtain. Neglect means deterioration into a state of extreme involution, ending either in death (from intercurrent disease or exhaustion) or in a relatively fixed state of under-development little ameliorated by any course of treatment at present known to us. Intelligent and careful treatment, on the other hand, leads to at least some degree of improvement and perhaps to a very striking betterment in nutrition and growth. Whether a child whose arrest of growth has lasted for five years, leaving him at the end of that time 50 per cent. below the average weight for this

age, can under any conditions be expected to develop into a man of average size, I am unable to say. That our methods of treating such cases fall short of the ideal is not improbable, and it may be that in children with extreme but uncomplicated infantilism the outlook for progress toward normal development would be considerably better than we can at present assert it to be, assuming that further improved methods should come into use.

From the cases observed by Dr. Holt and myself we have been instructed in several particulars relating to sequelae and complications. Case V of our group developed a high grade of simple anaemia which lasted several years; yet after so lasting the child began to grow in a promising manner despite the fact that the anaemia still persists. The fact is instructive as pointing to a dissociation of the causes of the anaemia and the causes of the retarded growth. No opinion can be ventured as to the ultimate influence of the anaemic state on the prognosis. In Case IV there was an early and marked anaemia, but this did not persist for more than a year, and as the nutritional conditions improved the haemoglobin rose from 35 to 61 per cent. In Case III anaemia was only moderate, and during the past two years there has been a gradual and fairly satisfactory growth of the body. In

Case II the improvement was very slow through many years, but recently has become remarkably rapid. With this rapid improvement in growth some errors were made in diet owing to a desire to push the gain by full feeding. This experiment resulted disastrously in that it was soon followed by *grand mal* epileptiform seizures, coming at short intervals. Two years previous to this outbreak the child had had a few short seizures of loss of consciousness without motor symptoms, and it now appears that these were probably examples of *petit mal.* The onset of *grand mal* seizures was attended here by a very considerable rise in the indications of intestinal putrefaction. I believe this case to be a clearly defined and unimpeachable instance of epilepsy developing as the result of cerebral irritative intoxication from putrefactive products absorbed from the intestine. I have long maintained that such cases occasionally arise, but it is seldom that the antecedent conditions are so well known to the physician as in this case. This case is thus in my judgment a singularly definite example of epilepsy arising from intestinal intoxication in a child with a nervous system rendered unstable by long intoxication of milder intensity than that needed to induce *grand mal* seizures. In this instance a rapid improvement set in with the institution

of very careful regulation of diet and environment, but the ultimate outcome of the epileptiform state cannot be predicted.

The Therapeutic Modification of the Bacterial Conditions in Intestinal Infantilism

The central aim in the treatment of infantilism is the modification of the bacterial flora of the intestine. There is no evidence that any therapeutic measures which do not exert some direct or indirect influence in this direction can be truly effective. To bring about an amelioration of the bacterial conditions in the intestine is a task of the utmost difficulty, calling for an understanding of principles, close attention to details, and painstaking care during a long period of time. In some important aspects there is a close similarity between the therapeutic requirements of intestinal infantilism and those of the extreme forms of chronic saccharo-butyric putrefaction associated with an infection by bacteria of the *B. perfringens* and streptococcus types. In both we have to deal with a chronic enterocolitis leading to failure in nutrition; in both the element of intoxication is prominent, and in both apparently trivial errors in diet are followed by temporary setbacks. There are, however, two highly significant differences between these types of infection, and both of

these differences make for a more favorable outlook in the case of the disease of childhood —at least so far as the prospect of life is concerned. One of these differences lies in the nature of the pathological process, the other in the circumstances attendant on childhood. The process in extreme saccharo-butyric putrefaction is one of very long standing, and probably leads to an impairment in the ability of the mucosa to regenerate adequately the excessively desquamated epithelium; it is questionable whether in infantilism the damage to the mucosa is ever so profound as this. And as regards the attendant circumstances of childhood there is the essential fact that the patient's age makes it possible to control with precision the conditions of his life, whereas in the extreme saccharo-butyric infections of adults the freedom of action possessed by the individual sooner or later leads him to make mistakes in his habits of life which lead to dangerous relapses and ultimately to death.

What I shall here write about the treatment of infantilism is based on the study of only a small number of patients, and for this reason, if for no other, will be incomplete. This, however, does not deter me from offering some definite advice in regard to treatment, for I believe that the experience gained from the highly detailed study of a few patients

will prove useful in the handling of this not very uncommon condition, by those whose opportunities for study have been less good than mine. I shall arrange what I have to say under the following headings:

General Hygienic Measures.
Dietetic Measures.
Pharmacological Measures.

General Hygienic Measures

In the care of the subjects of infantilism the hygiene of environment is of much importance in reinforcing the effects of more specific therapeutic measures. Two environmental requirements stand out sharply and require the consideration of the physician; first, a temperate, equable and fairly sunny climate, and, secondly, soothing human surroundings and limited companionship. In all marked states of infantilism the circulation is impaired and the loss of animal heat is a severe tax to the organism if there be prolonged exposure to cold. In Case II the cold months of winter were spent in a mild climate, which made it possible to be out of doors a large part of the day without excessive radiation of heat, and there is good reason to think this precaution was a material help in paving the way for the subsequent improvement in nutrition. In Case I it was impracticable to send the

child to a warm climate in winter, and the exposure to the winter's cold in New York seemed clearly an obstacle to quick improvement in nutrition. Except on the most inclement days the child should be out of doors for a time despite the drain on animal heat, for the alternative of remaining indoors is still more objectionable. It is especially in the summer months that these children tend to do badly. This is probably attributable mainly to the difficulty in securing food sufficiently free from objectionable bacteria during the hot months, but is doubtless due in part to the prostrating effects of prolonged exposure to a high temperature. By taking great care it is possible to avoid these common summer disturbances of digestion connected with hot weather, and this is in itself a very important advantage. Even in selecting a mild winter climate it is necessary to balance the advantages of mild weather against the dangers that arise from the inability to secure clean food.

It is essential that the attendant should be a person of more than ordinary tact, gentleness, good sense, patience and cheerfulness, for the subject of infantilism is often irritable, peevish and emotionally depressed and depressing. The patient should see visitors only seldom and only for a few minutes at a time. If permitted to play with other children he

should be with only one child at a time. The intoxication leads to so much physical and mental languor that it is inadvisable to attempt to teach these children in the ordinary ways. They can only be coaxed, very tactfully and cautiously, into an interest in numbers, letters and objects of various colors and shapes. Prolonged attention is undesirable and leads to extreme fatigue. These children are destined to be much retarded in the acquirement of knowledge, but as their natural intelligence is not distinctly impaired they can develop satisfactorily in a few directions. The illness of these unfortunate children is not without the compensation that they cannot be forced into the stupid conventional pleasures so commonly provided for children. To this and to the opportunity for quiet reflection I am disposed to attribute the noticeable thoughtfulness of most of the subjects of infantilism. When the stage has been reached in which there is a steady gain in weight, the periods of teaching can be increased. I believe that the ultimate mental growth of these children will be good in cases that are carefully managed. One patient of extreme type whom I have had under observation from time to time for ten years is now married and in good health. She is a well educated and cultivated person, but undersized.

The patients must be encouraged to take exercise daily, even if it causes fatigue. In experiments which I made on healthy young men who were intoxicated experimentally with indol, it was found that active exercise distinctly aided the subjects in overcoming the sense of great fatigue from which they suffered. This is probably to be attributed to the improved opportunity for oxidation which exercise affords. I have noticed the same effect of exercise on several adults with presumably indolic intoxication. But it is easy to overdo in exercise for these retarded children, and it is important to avoid excessive fatigue as it apparently acts unfavorably on the digestive processes.

Dietetic Measures

Dietetic measures are the keystone of the therapeutic arch in infantilism. Without the closest attention to them there is little chance of beneficially modifying the intestinal processes which underlie the affection. Cautious and prolonged experimentation is necessary to obtain the best dietetic conditions for each patient. The problem varies somewhat in different individuals and may vary for the same patient from time to time. It may be stated in the following general terms: to secure the absorption of foodstuffs adequate in quality

and quantity for the reasonably rapid growth of skeleton, muscles, blood and nervous system, with as little waste as possible from non-absorption and as little opportunity as possible for excessive putrefaction. If the absorption of foodstuffs be indeed adequate for the growth of bones, muscles and nervous system it is probable that it will suffice also for the growth of viscera and the production of sufficient fat. It is necessary to discuss separately the different types of foodstuffs in their relation to infantilism before considering any special dietary as a whole.

The Carbohydrates. It has been already mentioned that the carbohydrates are the obvious and fruitful cause of derangements of digestion that are clinically determinable, especially diarrhoea and flatulence. Probably by far the greater number of acute disturbances of digestion in the course of infantilism are referable to errors relating to the carbohydrates. I deem it impossible at present to speak with precision and fulness regarding the relative merits and demerits of the various carbohydrate foods with respect to infantilism. From a considerable, but by no means exhaustive, experience with various carbohydrate foods I have reached the conclusion that such carbohydrate food as can be taken by these patients is best given in the form of starch-

holding preparations, and not in any ordinary form of sugar. I have seen the best results from the use of well-boiled rice or arrow-root or cream of wheat, supplemented with a partly dextrinized preparation such as the Huntley and Palmer breakfast biscuits. Milk sugar, in the proportions in which it occurs in milk, may also be well taken, especially when a distinct improvement in nutrition is already in progress. I suspect that milk sugar is better tolerated than an isodynamic quantity of glucose or saccharose, but have no proof that this is so. Foods which contain an abundance of soluble carbohydrates, as Mellin's food or malted milk, cannot be recommended. Perhaps the most objectionable of all ordinary natural carbohydrate foods is potato, which can generally be counted on to occasion flatulence. The reason for this is not at present clear. In the severest forms of infantilism the total quantity of carbohydrates which can be tolerated may be very small, and it may be possible to supply less than one fifth of the calories required by the organism (instead of nearly one half as in health) in this way. An especial sensitiveness to carbohydrates may be developed during febrile attacks (as those due to taking cold), and it is then best to withdraw them entirely for a few days.

In every case of infantilism one of the most important and difficult tasks for the physician is to determine how much carbohydrate food his patient can utilize at a given time. The amount which is appropriate at one time may be less or more than can be tolerated at another. Where the patient can take a small quantity of carbohydrates it seems best to give it divided in the several kinds. Thus at one time in the day the child receives a Huntley and Palmer breakfast biscuit with minced beef or chicken or with beef juice; at another time he receives a portion of boiled rice with one or two ounces of milk, and at still another time he receives a larger portion of milk alone. It is unwise to concentrate the carbohydrates at one period; thus milk, rice and biscuit should not be given at one meal. If the allotted carbohydrates appear to be well tolerated (*i.e.* cause little or no flatulence, no marked softening of the stools, no increase of mucus and no increase of indican in the urine) it may be cautiously increased in amount. If the child has been receiving twenty grams of boiled rice at a feeding, the amount should be increased by five grams rather than by ten grams until a point is reached at which it appears, after a trial of several days, that the increased amount is not well tolerated (*i.e.* causes flatulence or abdominal discomfort or

slight diarrhoea or increase of indican). It may then be necessary to fall back to the original amount of rice, or it may be that a portion of the attempted increase can be maintained with advantage.[1]

In every experiment made with a view to establishing a diet the following cardinal rule should be observed: *the physician should vary only one article of diet at a time.* If more than one article of diet be varied at once the experiment will lack scientific precision and the best results cannot be attained. When a tentative diet is tried it should be so made up as to permit a definite gain in knowledge from intelligent successive variations in the amounts of the various foodstuffs employed. This careful and painstaking experimentation calls for much patience, but is rewarded by the fact that it leads to a gain in definite information. Haphazard, quick variations of

[1] I have made a few observations on the use of diastatic ferments as an aid in the digestion of carbohydrates, but such experience as I have had has been too unsystematic to permit any definite inferences as to the value of such enzymes. I doubt very much if their use materially influences the course of the affection or makes it possible to increase the carbohydrate food more rapidly than would otherwise be the case. This latter point, which is one of considerable practical importance, must be settled by well-planned experimental methods. In the meantime I think it well to give the patient the benefit of the doubt by employing small quantities of an active diastatic ferment, prepared in the dry form, as, for example, taka-diastase. The powder should be well mixed with the food at body temperature.

several factors simultaneously may accidentally give good results at times; yet in the long run there is a saving of time, for all concerned, if the physician takes the trouble to proceed more deliberately with the establishment of the dietetic treatment.

The Fats. The intestinal infections associated with infantilism call for the most careful regulation of the fat intake. This intake cannot be prescribed in any fixed and special terms, but only on the basis of a general principle. The principle to be obeyed is the following: give only so much fat as will in large measure be resorbed. The stools should not be permitted to continue voluminous and excessively fatty. The objections to this continual fat loss are mainly two—the unnecessary and harmful loss of calcium and magnesium soaps and the interference with digestion and absorption which is occasioned by the presence of fatty material, the latter tending to favor intestinal putrefaction. From the fact that calcium and magnesium are constantly lost as soaps it does not necessarily follow that if we prevent the alkali earth metals from being saponified we shall prevent them from being lost in the feces. We are still too ignorant of the conditions under which these elements are absorbed to form a judgment on this point. If we may judge from the case of healthy

children already cited, it is not unfair to assume that positive balances in calcium and magnesium are more likely to be attained by the reduction of the milk fat than through permitting the free use of milk fat. While I am not sure that we are justified in transferring these results on nearly healthy infants to the absorption in our cases of infantilism, it is obvious that at least there is a possibility of securing improved absorption if we check the persistent loss of soaps with the stools. Much more study is necessary to show us whether the alkali earth metals are normally absorbed in an important degree as soaps of these elements. Probably this is one of the most important ways of absorption for these metals and we should strive not to prevent saponification but to secure good soap absorption.

In any case of infantilism in which there is a continuous excessive loss of fat, the intake of fatty food should be gradually lowered until the feces no longer show the indications of such loss. When the level has been reached at which the movements are no longer homogeneous, but are made up of a conglomerate of small individual masses, the fat loss will not be excessive. From time to time the fat may be somewhat increased, for if the progress of the affection is favorable there will be a

gradual increase in the power of absorbing fat.

In Case I the relation between the intake of fat and the loss of fat in the feces was carefully determined by Dr. Wakeman for a period of eleven days, during which there existed an insignificant positive calcium balance, a very small retention of nitrogen and an essentially stationary weight. The daily intake of fat (neutral fats, fatty acids and soaps) amounted to 38.28 grams, the intake for the period having been 382.8 grams.[1] During the same period there was a daily loss of fats equal to 5.56 grams, or 55.6 grams for the period. The fat loss is here equivalent to 14.5 per cent. of the ingested fat. This is distinctly in excess of the normal fat loss, but does not represent extremely low fat absorption. The fat excess was sufficient to prevent the conglomeration of the feces. Two months before this period the absorption of fat was much less good with the same fat intake, for it reached at this time as high as 22 per cent., and even 25 per cent., of the ingested fat.

[1] These fats were distributed as follows:

Neutral fats	66.55 per cent.
Fatty acids	16.49 per cent.
Soaps	16.96 per cent.

The figure here given for soaps is doubtless too high, as other substances than fat must have found their way into the ether extract.

The fat loss was even larger than this at the time when the patient first came under observation, and on several subsequent occasions. On these occasions the fat intake was decreased to meet the poor absorption. Although the fat loss was as great as 14.2 per cent. so recently as three months ago, in Case I, I did not at this time make any further reduction in fat, as there was evidence of a slowly increasing power of absorption. Recently (June 1, 1908) I deemed it best to reduce the fat to 25 grams daily, and on this basis an entirely satisfactory absorption was secured. It should be noted that the relatively good fat absorption of recent periods in this patient does not represent the actual state of absorption until a period of general symptomatic improvement (without considerable gain in weight, though a forerunner to such gain) had set in.

The Proteins. On the use of the proteins in infantilism I have not as yet been able to obtain much specific information, as opportunities for thorough investigation of the effects of different types of proteins have been inadequate. In children under three years of age it is probably good practice to give the greater part if not all the proteins of the food as milk proteins. The conditions of digestion are apt to be such in infantilism that eggs are not well tolerated, but there is

no evidence that this is due to an intolerance of egg albumin, but rather that it is due to an intolerance for the constituents of the yolk. The question of the use of meat is one that comes up in every case in children over three years of age. In Cases I and II small quantities of meat were permitted during long periods of time as part of the protein food. There was no evidence of any detrimental effects from the cautious use of meat. On the other hand, there is also no positive evidence that the use of meat might not have been dispensed with, through the substitution of milk proteins. I have not been able to satisfy myself either in Case I or Case II that the cautious use of minced beef or minced chicken once daily has tended to cause greater putrefactive decomposition than was the case where milk proteins alone were used. But in both these cases there were periods when meat was allowed in excessive amounts, as indicated by symptoms of intoxication and unnecessarily abundant putrefactive products in the urine. A consideration which has had some influence in determining the use of meat has been the presence of iron in such food. The dietary in cases of infantilism tends to be low in iron and it has seemed desirable to make use of some meat rather than to use milk as the exclusive source of protein, but whether this

has really been effective in helping to overcome the anaemia nearly always present, it is impossible to say.

It has already been mentioned that the physician tends in the treatment of infantilism to give an excess of protein owing mainly to the difficulty in giving an adequate quantity of carbohydrates and fats. I have myself tended to make use of a greater quantity of protein food than has perhaps been wise. The tendency to give protein in relative excess was constantly noted in both Case I and Case II. It is only latterly that I have learned to replace in a measure the typical protein foods by the least objectionable form of protein—namely gelatin.

The Use of Gelatin. The use of gelatin as a foodstuff in bacterial infections of the intestinal tract has never received the attention it deserves. The physician is not infrequently confronted with a dietetic problem which consists in endeavoring to maintain nutrition under conditions where no combination of the ordinary proteins with fats and carbohydrates suffices to maintain a fair state of nutrition. The difficulty which most frequently arises is that every attempt to use carbohydrate food is followed by fermentative disturbances of an acute or subacute nature which delay recovery or even favor an existing infection to the

point of threatening life. The attempt to replace the carbohydrates in large degree by proteins is blocked by the serious difficulty that all the ordinary proteins, when given in amounts distinctly in excess of the habitual quantities, afford material for putrefactive decompositions which it is necessary to restrict. A great desideratum, therefore, is a food which, while readily undergoing absorption, shall furnish a supply of caloric energy and which at the same time shall be exempt from ordinary fermentative decomposition. Such a food exists in gelatin.

The exact nature of all the cleavage products of gelatin is not at present known.[1] Certain facts, however, stand out significantly. One is that gelatin contains no tryptophan nucleus and that it can hence yield neither

[1] The following figures (representing percentages) have been obtained for the composition of gelatin:

Glycocoll	16.5	Glutaminic acid	0.88
Alanin	0.8	Aspartic acid	0.56
Aminovaleric acid	1.0	Serin	0.4
Leucin	2.1	Lysin	2.75
Prolin	5.2	Arginin	7.62
Phenylalanin	0.4	Histidin	0.40

These figures have been obtained by Emil Fischer, P. A. Levene and B. H. Aders: Ueber die Hydrolyse des Leims. *Zeitschr. f. physiol. Chemie,* XXXV, p. 70, 1902. See also Emil Fischer and E. Abderhalden: Notizen über die Hydrolyse von Proteinstoffen, *Zeitschr. f. physiol. Chemie,* XLII, p. 540, 1904.

The absence of cystin from gelatin is noteworthy, though it is doubtful if it possesses any bearing on its use in the present connection.

indol nor skatol nor indolacetic acid nor indolpropionic acid. This fact makes it evident that no decomposition of gelatin that can occur within the intestinal tract can directly contribute to an intoxication in which the foregoing substances are concerned. A second peculiarity of almost equal importance is the fact that gelatin contains no tyrosin nucleus, even the relatively impure gelatin which is sold for cooking purposes giving only a slight and questionable reaction with Millon's reagent. The absence of the tyrosin nucleus in gelatin renders it impossible for paraoxyphenylacetic acid or paraoxyphenylpropionic acid to be formed in the course of bacterial decomposition of gelatin. In many chronic bacterial infections of the digestive tract paraoxyphenylacetic acid finds its way into the urine in excessive amounts. Similarly phenol arises in large part, perhaps exclusively, from the decomposition of tyrosin in the intestinal tract. It is thus evident that in any case of infantilism in which there is the usual evidence of excessive putrefaction, gelatin may be employed as a food without incurring any risk of increasing intestinal putrefaction in the directions just mentioned.

While gelatin does not contain either the tryptophan nucleus or the tyrosin nucleus, it gives a considerable yield of phenylalanin. It is possible that through oxidation of phenyl-

alanin in the body phenolic derivatives may be produced in slight amount (through hydroxilation of the aromatic nucleus), but the facts at the present time known relating to this point are opposed to this view.

Among the most important cleavage products of gelatin is glycocoll or amidoacetic acid. It has been recovered to the extent of 16½ per cent. of the original gelatin. Alanin is present in considerably smaller quantities. Leucin is also a not unimportant cleavage product. These monamino acids, together with the diamino acids, go to furnish a large part of the caloric value of gelatin. In this respect gelatin resembles other proteids. I do not know whether entirely satisfactory studies have been made of the caloric potential of gelatin furnished to the human body, but it may probably be regarded as not very different from that of protein in general, namely about 4.3 calories for one gram of gelatin. Assuming that the caloric value of gelatin is about four calories per gram, it is seen that 30 grams of gelatin (about 1 ounce) will yield the organism in the neighborhood of 120 calories. An ounce of gelatin can be taken without difficulty in 24 hours in the food of any child weighing not less than 28 to 30 pounds. This quantity of gelatin cannot, of course, be given at one meal, but may be so

scattered through the feedings for the day as to be easily introduced. It is obvious, however, that if owing to the practically complete resorption of this quantity of gelatin, a child receives 120 calories, this is an extremely important contribution to the entire caloric energy of the organism, since it may amount to from 10 to 12 or even 15 per cent. of the total requirements of the organism. It requires no argument to show that the difference between a child's being able to avail itself of 30 grams of gelatin daily and not being able to avail itself of it may make extremely important differences in its nutritional record. In younger children—children one or two years of age—smaller quantities of gelatin may advantageously be employed. It is not difficult to introduce from 10 to 15 grams daily of Cox's gelatin[1] into the milk or fermented milk of a child suffering from an acute intestinal infection.

On the theoretical basis which has just been brought out, we should expect to obtain certain results in practice. We may stop for a moment to inquire to what extent the results of practice have justified the use of gelatin in the food. Unfortunately I have no studies so conducted as to enable me to make an un-

[1] This is the form of gelatin which I have commonly employed. It may be mentioned that Dr. Wakeman found it to contain 0.74 per cent. of calcium oxide and a trace of magnesium.

equivocal inference that a gain in weight has been exclusively attributable to the addition of gelatin to the dietary, but I have observations on several carefully studied cases which make me think this probable. The case in which the evidence for this is most satisfactory is that of a child of two years with chronic infection with *B. bifidus* and *B. infantilis*. Here for a time the food consisted exclusively of kumyss, as all effort to give carbohydrate food caused exacerbations of diarrhoea. On this diet it was impossible to secure a gain in weight. The addition of 15 grams of gelatin daily was followed by a gain in weight, which ceased when the gelatin was stopped and again recurred when it was once more added to the kumyss. And it may be remarked in passing that such a combination of a fermented milk (thus largely ridding it from sugar) with gelatin seems to constitute the most appropriate treatment in some acute and subacute ileo-colic infections of childhood in which the intolerance for carbohydrates occasions a serious loss in weight and blocks the path to recovery. It is perhaps worth mentioning in this connection that both *B. bifidus* and *B. infantilis* may be regarded as practically uncultivable on ordinary gelatin media. We may reasonably ask ourselves if one of the advantages of gelatin as a food

may not be due in part to the failure of these and some other acidophile bacteria to grow on this type of protein.

It is somewhat helpful in formulating our indications for the use of gelatin to think of this food in its various substituent relations to the different types of foodstuffs. Given a full protein ration, it is probably true that either the carbohydrates alone or the fats alone may be substituted wholly by gelatin, perhaps not indefinitely, but for a considerable time. On the other hand, given average normal rations of fats and carbohydrates, the typical proteins may be replaced by gelatin, not wholly, be it noted, but only in part. To what extent these proteins can be substituted by gelatin has been much discussed and is still the subject of experimental inquiry. Any reliable general statement on this important point is at present impossible. Murlin[1] made an experiment on a man of 70 kilograms net weight and receiving a diet holding ten per cent. more than the fasting requirement of nitrogen and 51 calories per kilogram of potential energy, of which fully two thirds were supplied by carbohydrates. Under these conditions it was possible to supply 63 per cent. of the total nitrogen as gelatin for a period

[1] "The Nutritive Value of Gelatin," I. *Amer. Jour. of Physiol.*, XIX, No. iii, p. 285

of two days and still to maintain a small retention of nitrogen.[1] I do not know any pathological condition in which I would recommend the therapeutic use of gelatin in quantities and proportions even approximating those used in the experiment just mentioned. A certain disgust arises from the taking of large quantities of gelatin, and this in itself limits its use. It is doubtful if most adults can tolerate more than 50 grams of gelatin daily for a considerable period, and many cannot take more than 30 or 40 grams without developing a dislike. Thus we are in general limited in using gelatin to about 10 or 15 per cent. of the total caloric requirements. In using this proportion of gelatin as part of the dietary of a patient with infantilism it is always desirable to formulate a clear conception as to the reason for which it is given in the individual case—whether mainly to replace fats,

[1] It appears that the high percentage of glycocoll in gelatin may be an important factor in this retention of nitrogen, which is however only temporary. This temporary character of the glycocoll nitrogen retention may help to explain the inadequacy of gelatin as a substitute for typical protein food. See Murlin, "The Nutritive Value of Gelatin," II. *Amer. Jour. Physiol.*, XX, No. i, p. 234.

If one represents the protein metabolism in starvation by one the use of about the same quantity of gelatin reduces the protein waste of the body 23 per cent. (Kirchmann: *Zeitschr. f. Biol.*, XL, p. 54, 1900.)

In sparing protein small quantities of gelatin appear to have about as much effect as larger amounts.

carbohydrates or proteins. In a case where carbohydrates and fats are tolerated in fair amount without disturbance the use of gelatin should be regarded as a means of reducing the requirements of ordinary protein food with a view to limiting intestinal putrefaction based on the breakdown of tryptophan and tyrosin. On the other hand, where carbohydrates must be used sparingly or fats are badly resorbed, or where both these conditions prevail, gelatin should be utilized with a view to replacing in part either or both these foodstuffs, but without reducing the ordinary protein nitrogen below a fair average requirement.

Thus we may summarize as follows the qualities for which gelatin can be recommended as a foodstuff in cases of infantilism: (1) a considerable degree of caloric value, (2) as a partial substitute for carbohydrates, fats or common proteins, (3) as incapable of undergoing putrefaction based on the presence of the tryptophan or tyrosin molecules, (4) on account of prompt absorption, and (5) owing to its inability to support certain specific forms of bacterial life associated with this disease.

Finally, in reference to diet, the following example may be given. The following dietary was successfully employed in Case I during several critical months, that is, while the

transition was being made from a condition of stationary weight to one of uninterrupted gains in weight. This dietary was subsequently modified by reducing its content of fat by the addition of small quantities of whiskey and by some minor changes.

Breakfast, 6:30—7:00 A. M.	6 ounces milk with gelatin
	1 Huntley & Palmer biscuit
Lunch, 9:30 A. M.	6 ounces milk with gelatin
	2 Huntley & Palmer biscuits
Dinner, 1:30 P. M.	Scraped beef and juice (one tablespoonful of each)
	1 tablespoonful vegetable*
	1 tablespoonful rice
	1 Huntley & Palmer biscuit
Afternoon Lunch, 4:30 P. M.	6 ounces broth with gelatin
Supper, 6:30 P. M.	1 tablespoonful rice
	6 ounces milk with gelatin
	2 Huntley & Palmer biscuits

Total quantity milk daily, 18 ounces
Total broth daily (beef tea, chicken or mutton broth), 6 ounces
Total rice daily, 2 tablespoonfuls
Total Huntley & Palmer biscuits daily, 6
Total gelatin daily (Cox's), 1 box (about 1 ounce)
Beef juice from 1 lb. round of beef, daily

I have calculated that the caloric value of this dietary is approximately as follows:

Fat	342 calories
Proteins	205 calories
Gelatin	120 calories
Carbohydrates	480 calories
	1147 calories

*The vegetables used were spinach, string beans, carrots and peas. It was necessary at times to eliminate these vegetables entirely from the dietary for short periods of time, as they act in an irritative way.

These figures are based on the assumption that the patient got in this dietary 38 grams

of fat, 8 grams nitrogen in the form of proteins, other than gelatin, 30 grams gelatin, 27 grams milk sugar, and from 90 to 100 grams of starch and dextrine, in the form of Huntley & Palmer biscuits, rice, vegetables, broths, etc. The assumption that the caloric value of this diet is about 1150 calories cannot be far from the truth. By changes subsequently made and mentioned above, this caloric value was reduced to about 1100 calories.

I am inclined to think the above dietary might be criticized as containing an excess of proteins. The excess is, however, much less now than when the patient first came under observation, for it is obvious that an excess of proteins for a child weighing 25 pounds is considerably less excessive for a child weighing 31 pounds. I am, however, disposed to think that the protein is still from 20 to 25 per cent. in excess of an ideal diet, but I have not reduced it simply because the patient is doing so well that I am disposed to let well enough alone. I shall, however, consider it proper to make a slow reduction in the proteins if I cannot otherwise satisfactorily reduce the quantity of putrefactive products in the urine.

Pharmacological Measures

Although pharmacological measures do not have a large share in the treatment of intes-

tinal infantilism there are a few topics which require at least a mention in this connection. These are the use of iron, the use of alcohol, the employment of cathartic and antiseptic medicaments and the administration of calcium and magnesium salts and of phosphoric acid. I believe that in general iron preparations are not well tolerated by the stomachs of these patients and that it is better to avoid their use. It is also to be questioned whether iron is helpful for the amelioration of the associated anaemia. It is certain that the anaemia may greatly improve as the result of the institution of a suitable diet, without the aid of drugs. The objection to the use of iron appears to me extremely well defined during the period of absolute arrest of growth. When growth has begun anew and is progressing in a satisfactory way iron preparations may be employed with benefit to a persistent anaemia, and even without noticeable detrimental effect on digestion. It is desirable to employ the least irritant preparations and to desist promptly when increased digestive disturbances occur.

The administration of from 5 c.c. to 10 c.c. of whiskey with the milk, kumyss or broth may prove a helpful measure where the hands and feet are persistently cold and the peripheral circulation is feeble. In warm weather the alcohol should be omitted except, perhaps,

in the morning. The doses just mentioned may be repeated three or four times daily in some instances.

As to the use of cathartics it is certain that they should always be sparingly employed and not frequently. It is not clear that they accomplish any unmixed good. Small doses of calomel may be used from time to time to bring away the considerable quantities of mucus which accumulate in the upper colon or to bring away putrefactive products which have been suspected to accumulate. The good that is accomplished by such evacuations is commonly balanced in part by some prostrating effect of the cathartic and the disturbance of regular intestinal habits. I am disposed to believe that the chief legitimate use of cathartics arises when there has been an error of diet, but as such errors are very largely avoidable, the resort to cathartic medicaments should be rare. Where the rapid diminution of putrefaction is required, a quickly acting cathartic, such as castor oil, is probably the most effective remedy. I have little faith in the use of intestinal antiseptics in the management of infantilism and think we should avoid experimenting with them, at least until we get a more rational basis for their use than at present exists, and can feel assured that those we try are harmless. Yet it is possible the

future will teach us something about the rational use of suitable antiseptics.

Where defective absorption of calcium and magnesium is so conspicuous a feature as in the processes underlying infantilism, it becomes essential for us to inform ourselves fully as to the conditions that promote the absorption of salts of the alkali earths. At present our knowledge on this important point is far from satisfactory. What can we do to secure better absorption of lime and magnesium salts? I have already indicated my belief that those conditions which mitigate the inflammatory state of the small intestine are those that lead to spontaneous improved absorption. But we may not be able to wait patiently for this improvement; we may feel obliged to do something to secure a larger absorption of salts by offering the mucous membrane of the intestine a larger or wider choice of alkali earth compounds. Physicians frequently do in fact attempt this. One way of so doing is by giving the patient those salts which occur in the bones, especially the phosphates and carbonates of calcium and magnesium. As to the efficacy of such attempts we know nothing definite, but are warranted in suspecting that they are largely futile. Since the feces contain an excess of phosphates of the alkali earths in infantilism, it is clear that the intestine must have chances

to take up these salts, but fails to use them. In healthy young dogs (and presumably in children) the normal mucous membrane apparently takes up inorganic tricalcium phosphate as well as the calcium salts of milk.[1] But under the pathological conditions of infantilism there is no reason to suppose that calcium phosphate would have any different fate from the calcium salts of the milk, which we know to be imperfectly absorbed. Possibly one factor in the defect of absorption is the failure of the gastric juice to secrete hydrochloric acid in adequate quantity,—a function which must facilitate the absorption of calcium and magnesium through the gradual formation of the chlorides. However this may be in fact, we shall do well to give our alkali earth salts in soluble form. For this purpose the lactates of calcium and magnesium may be used. From 20 to 40 milligrams of calcium lactate may be given in aqueous solution in the food three times daily without any detrimental effects. I do not think we are justified in stating positively that this is a truly efficacious method of securing an improved absorption in marked cases of chronic enteritis, but it probably is the best method at our disposal. It deserves

[1] Hans Aron and Karl Frese. *Biochem. Zeitschr.*, IX, pp. 185-207, 1908.

to be experimentally worked out with the utmost care.

Finally a word should be said on the administration of phosphoric acid. It is as important to give phosphoric acid as to give calcium and magnesium where the skeleton is retarded, but the acid should be given separately from the alkali earths in order to avoid the precipitation of insoluble phosphates in the lumen of the gut. Where the stomach is not sensitive the acid sodium phosphate may be given, but where this difficulty does exist the dilute phosphoric acid may be given before meals.

I shall not attempt to discuss here the use of fermented milks because I do not at present possess the necessary data. I am, however, making experimental observations on this subject and hope before long to consider it systematically.

It is believed that the foregoing considerations regarding the pathology and management of intestinal infantilism justify the conclusion that the outlook for the amelioration of extreme cases of this affection is in reality much better than might be supposed from the results commonly obtained. The task of management is at best a tedious one, but it is one which repays deliberate effort, both in the variety of scientific interest it affords and in the satisfaction it yields through its practical successes.

It is essential to realize clearly that rapid recoveries are not to be expected under any circumstances, after a state of true infantilism has been developed. Moreover it will be a help to recognize that the process of recovery may very properly be regarded as made up of two distinct stages. The first stage is one of improved nervous and digestive conditions, with signs of diminishing intoxication. In this stage there is little or no gain in weight although there may be a slight improvement in strength. This stage may last from three months to a year. At the end of this time the patient begins to gain distinctly in weight as well as to continue growing in strength, and when this occurs an uninterrupted improvement may be reasonably looked for. The important thing is to understand that improved bacterial conditions must precede by a considerable time a significant gain in weight.

Conclusions

In view of the many details which it has been necessary to incorporate in this study of infantilism, it seems to me desirable to summarize the chief conclusions which may be drawn.

The following are the facts which I would especially emphasize:

1. There is a pathological state of childhood marked by a striking retardation in growth of the skeleton, the muscles and the various organs and associated with a chronic intestinal infection characterized by the overgrowth and persistence of bacterial flora belonging normally to the nursling period. To this condition may be applied the term Intestinal Infantilism.

2. The chief manifestations of intestinal infantilism are arrest in the development of the body; maintenance of good mental powers and a fair development of the brain; marked abdominal distension; a slight or moderate or considerable degree of simple anaemia; the rapid onset of physical and mental fatigue; irregularities of intestinal digestion resulting in frequent diarrhoeal seizures. Clinical features of secondary importance are excessive appetite, various minor signs of nervous instability, a subnormal temperature, cold hands and feet, and slight signs of rickets.

3. A study of the bacterial flora of the intestinal tract in cases of infantilism shows that the dominant bacteria of the upper and lower colon and probably of the ileum are largely Gram-positive organisms belonging to the groups of organisms which may be designated as the *Bacillus bifidus* type, the *Bacillus infantilis* type and the coccal type. It is

impossible to say to what extent *B. bifidus* and *B. infantilis* constitute the dominant types, partly because of the difficulty in forming reliable estimates of the quantitative relations between these organisms, partly because they vary in the same individual under different conditions of diet and at different stages of the disease. Noteworthy is the absence of organisms of the *B. coli* and *B. lactis aerogenes* type, not only from the feces but from material collected through the use of a cathartic. The dominance of these Gram-positive organisms relates, however, only to infantilism in its incipiency and at its height.

4. Among the urinary expressions of the bacterial state associated with intestinal infantilism is to be constantly found an excess of putrefactive products of intestinal origin. Prominent among these are indican and phenol compounds. At times indolacetic acid is a prominent putrefactive product. Sometimes the aromatic oxyacids are much in excess.

5. Among the characteristic features relating to the intestinal contents are the presence of neutral fat, fatty acids and soaps in marked excess, pointing to impaired fat absorption. With this condition is associated usually an increase of mucus and other evidence of excessive desquamation of epithelial elements.

6. A careful study of the calcium and magnesium balances in one of our cases (Case I) showed failure of normal resorption of calcium and magnesium, thus accounting for the failure of skeletal growth. The amount of calcium lost by the feces as soaps of calcium was sufficient to have furnished a fair skeletal growth had these calcium soaps been absorbed instead of lost. It is a practical certainty that the loss of calcium and magnesium through the feces is the explanation of the impaired skeletal growth in intestinal infantilism.

7. In the pathology of intestinal infantilism two leading features call for explanation—first, the retardation of growth; second, the chronic intoxication. The retardation in growth can apparently be explained on the basis of the imperfect absorption of nutritive material which can be demonstrated in these cases. This impaired absorption of foodstuffs is probably to be ascribed to a chronic inflammation located in the ileum and colon and associated with the presence of abnormal forms of bacteria. The intoxication which is so prominent a feature of intestinal infantilism at its height may confidently be ascribed to the action of putrefactive products of intestinal origin upon the central nervous system and muscles. The exact relation of the abnormal bacterial flora to the pathological conditions in the in-

testine is not yet clear. The chief evidence in favor of the causal relationship between the phenomena of infantilism and the overgrowth and persistence of flora of the nursling period, especially *B. bifidus*, is found in the changes that occur during convalescence when these organisms are gradually replaced by those of the type appropriate to childhood. A further evidence in the same direction is seen in the great increase in the infantile types of bacteria during periods of relapse. There is no evidence at present that intestinal infantilism has any other origin than a purely intestinal one.

8. There is a condition of acute or subacute infection of the intestinal tract in early infancy which leads to great losses in weight and strength, the persistence of which is a probable cause of chronic infantilism. This condition, like chronic infantilism, is associated with the dominance of Gram-positive microörganisms in the intestinal tract, mainly those belonging to the groups of *B. bifidus* and *B. infantilis*, or certain other acidophile bacteria which are closely related. The bacterial conditions of this acute or subacute infection, if not identical with those of chronic infantilism, are nevertheless very similar, and this is a further reason for regarding the chronic condition as

the outcome of the more acute state just mentioned.

9. The state of intestinal infantilism is a very persistent one and not likely to be followed by normal growth except as the result of careful therapeutic interference. A certain proportion of such infantilism children die from acute infections of the intestine; others are permanently retarded in growth, which leads to pronounced dwarfism.

10. Rational therapeutic interference in cases of chronic intestinal infantilism offers hope of the reëstablishment of the processes of growth even in cases in which the bodily arrest has been extreme and of long duration. If it is too much to say that the most satisfactory methods of treatment are now known, it may be claimed, at least, that we are in possession of certain principles of treatment which, when carefully applied, are likely to yield better results than any that have heretofore been employed.

11. Temporary relapses are very common in the course of this disease, even when great care is being taken to prevent them. The most frequent cause of such relapses is the attempt to encourage growth by the use of increased amounts of carbohydrates. When a relapse occurs the feces become voluminous, lose their conglomerate appearance and become

of lighter color. They show the presence of coccal forms in excessive numbers and there is in persistent relapses a return of *B. infantilis* and *B. bifidus*. Any disturbance of digestion which checks growth or causes loss in weight is to be accounted a relapse.

12. A permanently undersized individual is the outcome, even in the most favorably progressing instances, of the severe form of infantilism. This condition is not incompatible with a high degree of mental development.

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